Clinical Commentary

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The Physiological Basis of Cervical Facet-Mediated Persistent Pain: Basic Science and Clinical Challenges

Neck pain is common and has emerged as a worldwide leading contributor to years lived with disability over the past 2 decades.102 Neck pain often becomes chronic, with a 12-month prevalence ranging from 30% to 50%. Moreover, individuals who have worsening neck pain also show poor measures of health-related quality of life. At each spinal level from the cervical to the lumbar spine, there are bilateral synovial facet joints between adjoining vertebrae. In the cervical spine, these joints are a common source of neck pain and are susceptible to injury from trauma or during spinal degeneration.

SYNOPSIS: Chronic neck pain is a common condition and a primary clinical symptom of whiplash and other spinal injuries. Loading-induced neck injuries produce abnormal kinematics between the vertebrae, with the potential to injure facet joints and the afferent fibers that innervate the specific joint tissues, including the capsular ligament. Mechanoreceptive and nociceptive afferents that innervate the facet have their peripheral terminals in the capsule, cell bodies in the dorsal root ganglia, and terminal processes in the spinal cord. As such, biomechanical loading of these afferents can initiate nociceptive signaling in the peripheral and central nervous systems. Their activation depends on the local mechanical environment of the joint and encodes the neural processes that initiate pain and lead to its persistence. This commentary reviews the complex anatomical, biomechanical, and physiological consequences of facet-mediated whiplash injury and pain. The clinical presentation of facet-mediated pain is complex in its sensory and emotional components. Yet, human studies are limited in their ability to elucidate the physiological mechanisms by which abnormal facet loading leads to pain. Over the past decade, however, in vivo models of cervical facet injury that reproduce clinical pain symptoms have been developed and used to define the complicated and multifaceted electrophysiological, inflammatory, and nociceptive signaling cascades that are involved in the pathophysiology of whiplash facet pain. Integrating the whiplash-like mechanics in vivo and in vitro allows transmission of pathophysiological mechanisms across scales, with the hope of informing clinical management. Yet, despite these advances, many challenges remain. This commentary further describes and highlights such challenges. J Orthop Sports Phys Ther 2017;47(7):450-461. doi:10.2519/jospt.2017.7255

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The pathology associated with those tissue injuries includes microstructural damage to the collagen fibrous matrix of the capsular ligament, synovial fold pinching, and/or degenerative changes to the articular cartilage, which can lead to osteoarthritis. Because the facet joints are innervated by mechanoreceptive and nociceptive afferent fibers, any abnormal loading of the facet joint can also generate forces that mechanically load those afferents and initiate a host of pathophysiological responses that can lead to pain.

In particular, injury of the innervated ligament tissue that encapsulates the synovial joint has the potential to generate pain. As such, this commentary focuses on the physiological mechanisms by which biomechanical loading of the facet capsule can lead to pain, and the challenges in defining relevant thresholds for pain, biomechanical tissue injury, and neuronal responses, by integrating findings from basic science studies to inform the clinical management and/or diagnosis of whiplash-mediated facet pain.

When considering pain responses, it is always necessary to recognize that the sensory and emotional experiences of pain play a role in the clinical presentation.

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remain a major challenge. The afferent nerve fibers that innervate the facet joint and its capsular ligament have cell bodies in the DRG and synapse with neurons in the spinal dorsal horn. Nociceptive information is encoded by many types of afferents, including IB4-positive nonpeptidergic neurons and peptidergic fibers that produce neuropeptides, such as CGRP and substance P. Noxious stimuli are translated into electrical (eg, action potentials) and biochemical (eg, neurotransmitter) signals. In persistent pain, central sensitization occurs, with neuronal hyperexcitability and altered neurotransmitter production and release in the spinal dorsal horn. Abbreviations: CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; IB4, isolectin B4.

In humans, clinical assessment of both evoked and spontaneous sensory (eg, sensitization) and emotional pain symptoms may be performed using a variety of quantitative sensory testing methods and also with patient questionnaires. These studies have identified the complex physical and psychological clinical presentation of whiplash and inferred relationships between the traumatic injuries sustained in whiplash and the clinical symptoms that develop. However, clinical studies of the symptoms of facet-mediated pain and whiplash are limited in their ability to inform about the physiological mechanisms underlying pain onset and/or maintenance. The same pain symptoms evaluated clinically have been shown to be detectable and robust in animal models, and are especially useful considering the well-established dermatomal mapping that has been defined across a number of species. As such, in vivo models provide useful platforms to integrate assays defining mechanisms, physiology, and symptoms to define and understand painful injury and whiplash. Given the ability to study the physiological mechanisms of facet-mediated pain in vivo, the majority of studies throughout this commentary focus on findings in the rodent.

Although rodent models are useful in defining the pathophysiological mechanisms involved in the initiation and maintenance of facet-mediated pain, they are quite distinct from human models. An important distinction between species is their life span, which must be considered to understand the effects of timing between injury and symptom presentation in the human. Given
the typical life span of the rat, 13 days is equivalent to 1 human year.92 This relationship varies with developmental age in the rat. During adolescence it is approximately 10 days, during adulthood it is more like 12 days, and it is 17 days in the aged rat.83 In patients with whiplash, pain symptoms can develop within hours after injury.59,64,92 Although pain can resolve in some patients within 3 months, symptoms that last longer than 3 to 6 months are taken as chronic.3,54,77,83 Given the relationship between the age of the rodent and that of the human, approximately 2.5 to 4.5 rodent-days correspond to 3 months in the human, and approximately 5 to 8.5 rodent-days correspond to 6 months in the human. This temporal scaling means that findings in the rodent that occur after 5 days of injury simulate the time when pain transitions from acute/subacute to chronic in the human. Further, pain in the rodent lasting more than 8.5 days has likely transitioned to the chronic stage. Although rodent models are valuable in providing controlled investigations into relationships between injury, pain, and molecular and chemical mechanisms throughout the various stages of the development of whiplash pain, none has investigated the long-term disability associated with whiplash.

To understand the physiological basis of facet-mediated pain in a clinical context, pain symptoms of individuals with whiplash are briefly reviewed, followed by a discussion of their manifestation after excessive facet stretch in the rat. In the next section, the macroscopic kinematics and microscopic tissue injury of facet tissues are discussed as they occur during whiplash and simulated painful whiplash injury. The effect of excessive mechanical injury on neuronal responses is then reviewed in the context of both in vivo and in vitro models. Finally, several challenges of integrating biomechanical and neuronal findings across scales and species are presented, with a focus on both translation of biomechanical and physiological injury thresholds and the difficulties introduced by the heterogeneities of the facet anatomy.

**Pain Symptoms**

In patients, pain symptoms present as early as a few hours after whiplash injury, and persistent pain has been reported for up to 2 years after exposure.59,64,92 Patients with whiplash injury exhibit both focal and widespread hypersensitivity during quantitative sensory tests, including decreased pain thresholds in response to mechanical and thermal stimuli.91,92,93 Those individuals who go on to develop persistent pain show signs of altered central pain processing, like diffuse mechanical hyperalgesia, thermal hyperalgesia, and/or lower thresholds to painful electrical stimulation, as early as 1 month after injury.21,31,92,93 Patients with chronic pain exhibit primary mechanical hyperalgesia over the back of the cervical spine, in a “coat hanger” distribution indicative of peripheral nociceptor sensitization.21,81 These patients are also hypersensitive to pressure, heat, and cold stimuli at sites distant from the cervical spine, including over the median, radial, and ulnar nerve trunks in the arm and over the tibialis anterior muscle.81 Together, these studies demonstrate that generalized and widespread secondary hypersensitivity is robust in individuals who sustain a whiplash-like exposure and indicative of central sensitization. Due to the large scope of that literature, it is not described in entirety here, but there are other sources in which this is reviewed extensively.20,21,99

In addition to the evoked measures of sensitization, whiplash-like exposures can induce spontaneous pain that is also suggestive of central sensitization. Patient-reported sensory disturbances include spontaneous pain that is proportionate to and/or occurs in the absence of any inciting event.7 The inability to control such spontaneous pain is a primary motivator for individuals postwhiplash to seek medical care. The Neck Disability Index (NDI) is one of a variety of patient questionnaires used to quantify whiplash pain symptoms, including measures of self-perceived pain and disability associated with neck pain.101 Poor and chronic clinical outcomes are associated with baseline NDI scores greater than 30/100.30,93 More recently, NDI scores greater than 30/100 (or 15/50) have also been identified as a predictor and significant risk factor of poor patient outcomes.101 In a study of patients with whiplash, those with a baseline NDI score of greater than 30 also showed signs of generalized hypersensitivity, suggesting a relationship between nonevoked spontaneous pain and central sensitization.92 Because individuals postwhiplash present with symptoms of both evoked hypersensitivity and spontaneous pain, both of these aspects must be considered in animal studies.

Stretch injury of the facet capsular ligament comparable to that experienced during neck loading from a whiplash exposure induces symptoms in the rat that mimic clinical pain within 1 day following the joint injury and that persist for 3 to 4 weeks53,54 (FIGURE 2A). A whiplash-like stretch injury to the facet joint induces sensitivity to mechanical stimuli over the back of the neck,25 in the same “coat-hanger” distribution observed clinically.21,81 In addition, more widespread sensitivity is also produced; mechanical hyperalgesia is observed with a decrease in paw withdrawal threshold to von Frey stimulation, lasting for 4 weeks (FIGURE 2A). Moreover, thermal hypersensitivity can be produced in the rat (FIGURE 2B). Although spontaneous pain cannot be self-reported in animals, several observational methods have been developed to assess it, including evaluating facial expressions and/or grooming behavior, analgesic self-administration, and autotomy.50,61 The Grimace Scale uses facial expression assessment to detect spontaneous pain across a variety of species, including in mice,50,52,60 rats,15,24,65,68,87 and cats,35 and evaluates 4 different facial features that are rated on a severity scale of: 0 (not present), 1 (moderate), or 2 (present and severe) (FIGURE 2C).50 The Grimace Scale has been reported to detect spontaneous pain in rodent models of neuropathic pain.24,65 Although the Grimace Scale has recently been shown to have the resolution to detect pain from injection of the inflammatory mediator.
nerve growth factor into the facet joint (FIGURE 2C), it has yet to be investigated for use after a mechanical facet injury. Given the prevalence of spontaneous pain in individuals with whiplash, developing robust and sensitive methods to evaluate spontaneous pain in animal models would provide translational value. Rodent studies have shown that varying the severity of mechanical facet joint injury (ie, the magnitude of facet capsule stretch) directly affects the development and severity of pain symptoms. Supraphysiologic capsular stretch matching that of whiplash-like magnitudes is required to induce pain, but stretch at magnitudes comparable to those experienced during physiological joint loading does not induce pain. Although capsular stretch induces pain symptoms that are magnitude dependent, pain is not further increased if the capsule undergoes failure. These behavioral studies demonstrate that an intact facet capsule is required for pain development, which supports the notion that afferent fiber signaling is requisite to transmit sensory information from the periphery to the CNS (FIGURE 1). Together, in vivo and clinical studies of facet injury have found that aspects and consequences of subfailure biomechanical loading to the intact facet capsule have critical contributions to pain development. As such, nociception may be driven by the transduction of the multiscale tissue and joint kinematics to physiological cascades of resident afferents.

Kinematics and Facet Tissue Injury During Whiplash
The macroscopic kinematics, or motions, of the cervical spine during whiplash exposures have been extensively studied using both human in vivo and cadaveric in vitro methods and demonstrated that the spine undergoes a characteristic “S-deformation.” During a motor vehicle collision, this abnormal deformation is induced approximately 60 to 100 milliseconds after vehicle impact due to the torso moving forward and upward prior to the movement of the head. It is only approximately 85 to 140 milliseconds after the initial vehicle impact that the head rotates backward, before both the head and torso rebound forward due to the support of the seat and headrest, and decelerate following the impact.

Although the cervical spine has been shown to not undergo supraphysiologic intervertebral rotation during such exposure, local tissue injury has been defined to result from abnormal kinematics...
between vertebrae.\textsuperscript{6,67} As such, whiplash exposures can increase the loading of the individual tissue structures in the spine, and particularly the facet joint. In addition to directly loading and damaging the facet capsule via tensile loading, cartilage and synovium deformations have also been reported.\textsuperscript{72,74,84,108} Mechanical facet capsule loading, in addition to having the potential to load nociceptive afferents embedded in it, also produces laxity under some conditions that produce pain.\textsuperscript{60,70}

All of these local tissue–loading environments have the potential to result in joint instability, which can lead to other alterations in the kinematics of the overall joint and its capsular ligament during normal activities.\textsuperscript{41}

Maximum principal strains quantify the greatest relative deformation in a tissue and are estimated using changes in the tissue configuration. Strain is a unitless metric that is often measured using imaging of materials while they are under load. Biomechanical thresholds for tissue loading have been established for pain in the cadaver and in animal systems by measuring strains across the facet capsule. In the rat, supraphysiologic (approximately 20%–30%) strains imposed during dynamic facet capsule stretch at a rate of 500%/s, which matches that sustained by humans,\textsuperscript{66,90,95,113} consistently induced pain, while those in the physiologic range (approximately 6%–15%) did not induce pain.\textsuperscript{26,27,29} Of note, the strain magnitudes that induce pain in vivo are lower than the biomechanical strains at failure of the facet capsule, which have been reported at approximately 35% in posterior retraction\textsuperscript{84} and approximately 65% in distraction.\textsuperscript{108} Though large variability exists between subjects. This is not surprising given that complete transection of the capsule, simulating rupture, does not produce sustained pain in vivo.\textsuperscript{106} Indeed, this is consistent with the lack of capsule ruptures in cadaveric studies of whiplash simulations.\textsuperscript{33,66,67,111}

In this way, modeling specific scenarios of facet capsule stretch in vivo has provided complementary supportive evidence that an intact capsule is required for pain generation, an assertion that was previously only hypothesized from cadaveric simulations.

Full strain-field measurements across the surface of the human cadaveric facet capsule and in vivo in the rat exhibit heterogeneity during both physiological flexion/extension and joint retraction, simulating whiplash exposure (FIGURE 3A).\textsuperscript{72,74,84,108} Because strain magnitude has been shown to directly relate to the potential for and extent of pain, a heterogeneous strain field throughout an innervated capsule may also have variable potential for activating afferents, or at the least present heterogeneous afferent activation. Anatomical studies of the facet capsule evaluating the macroscopic and microscopic matrix composition and orientation of those components have shown that the facet capsule is composed of an outer layer of primarily collagen fibers oriented across the facet joint, while in its inner layer there are more randomly orientated elastic fibers.\textsuperscript{111,112} The thickness of the outer layer of the capsule, and the length of the collagen fibers within it, vary with the anatomic location of the capsule, as does the proportion of elastic fibers within in the collagen matrix.\textsuperscript{111,112} Because the microstructure of the capsular ligament dictates the biomechanical function and potential for injury, any variation in capsular microstructure likely corresponds to the functional ability of the capsule to guide and limit motions of the facet joint.

The greater proportion of elastic fibers in the postero-inferior aspect corresponds to the large strains that are sustained in that region during extension and the potential for recovery to the neutral position with minimal risk of impingement.\textsuperscript{90,111-113} Considering this close interplay between the local tissue structure and the function of the facet capsular ligament, a model of how local damage may occur due to abnormal whiplash facet kinematics emerges. Furthermore, with altered local loading, as has been corroborated by the altered local strains, it is likely that capsule damage can still occur, despite strains remaining below the catastrophic failure threshold of 35% to 65%. However, the heterogeneous structure of the facet capsule also makes it challenging to determine local damage based on strain, because relationships between strain and damage are not necessarily correlative.

The complexity introduced by the heterogeneity of the facet capsule’s kinematic response to load has led to work specifically assessing the local alterations in the ligament’s microstructure. Quantitative polarized light imaging is an optical technique that exploits the natural birefringent optical property of collagen molecules to quantify the dynamic reorganization of collagen fibers during mechanical loading, and has been used extensively to evaluate soft tissue biomechanics and other collagenous tissue equivalents.\textsuperscript{49,76,79,89} Using this approach, collagen fiber realignment during tensile and posterior retraction loading of isolated human cadaveric facets, and tensile loading of isolated rat facets, has been defined.\textsuperscript{70,72,74-76} In particular, those studies collectively demonstrate that areas with the highest fiber realignment correspond to those regions with microstructural damage to the collagen matrix (FIGURE 3B). These studies have shown that areas of greatest fiber realignment are significantly correlated with subsequent rupture,\textsuperscript{70,72,76} but do not necessarily correspond to areas of peak maximum principal or shear strain.\textsuperscript{72,76} Together, these findings suggest that collagen realignment may be a more sensitive indicator of microstructural injury than strain measurements, and further highlight the possibility that afferent fibers may be more susceptible to activation if they reside in regions where the collagenous matrix undergoes abnormal deformation. Nevertheless, fiber realignment is correlated with areas in the ligament in which there is unrecovered strain after whiplash-like loading.\textsuperscript{74} This spatial association supports the hypothesis that local changes in microstructural organization induced by loading known to be painful may contribute to the altered mechanical function of facet tissues. Fur-
ther, such deformation(s) of the matrix in a neuron's local environment may contribute to and/or drive nociceptive signaling from the joint.

To identify a single best predictor of microstructural damage in the facet capsular ligament remains difficult. Nevertheless, the studies highlighted here suggest that if laboratory research could focus on elucidating mechanisms of microscopic mechanosensation within the capsular ligament, then the broader basic science and clinical communities could better identify a biomechanical predictor for painful injury. Last, although the focus of this commentary has been on how the biomechanical environment can drive nociception, facet-mediated pain also can be induced by degenerative states. A host of biochemical cascades are initiated during joint degeneration that can induce degradation of facet tissues, including the articular cartilage and the capsular ligament (FIGURE 3C). Understanding the relationships between degeneration, nociception, and the onset of pain would also inform the mechanisms underlying injury-induced facet pain, because degeneration-associated tissue degradation has the potential to result in the altered kinematics discussed here.

**Neuronal Responses to Excessive Stretch**

Stretching the facet capsule beyond its physiologic limit can lead to altered physiology and morphology of the afferent neurons within the capsule, including changes in neuronal hyperexcitability and altered expression of neurotransmitters and other nociceptive molecules, both of which can contribute to pain (FIGURE 1). Excessive strains that induce behavioral hypersensitivity also induce electrophysiological changes in neurons during and after capsular stretch. For example, low- and high-threshold mechanoreceptors identified in the facet joint of the goat are activated by strains of 10% to 15% and 25% to 47%, respectively. It has been shown that strains above 38% ± 12% induce afterdischarge in the neurons facet capsule exceeding physiologic strains is sufficient to damage the ligament's microstructure and induce pain. As such, characterizing the functional changes of neurons and understanding their relationships to the local injury mechanisms during loading below the tissue failure threshold are important, and many studies have initiated these investigations using both in vivo and in vitro models.

The primary afferents that innervate the facet joint and its capsular ligament respond to different thresholds for activation by mechanical stimuli. A host of biochemical cascades are initiated during joint degeneration that can induce degradation of facet tissues, including the articular cartilage and the capsular ligament (FIGURE 3C). Understanding the relationships between degeneration, nociception, and the onset of pain would also inform the mechanisms underlying injury-induced facet pain, because degeneration-associated tissue degradation has the potential to result in the altered kinematics discussed here.

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**FIGURE 3.** Biomechanical measurements, imaging measures of microstructural realignment, and histological assessment of the cervical facet joint. (A) Schematic of a C1-C3 human cervical spine specimen in a test system with vertebral markers projecting anteriorly and a grid of markers attached to the C2-3 facet joint for kinematic analysis of the capsular surface strains during loading. The grid on the capsular surface is tracked by 2 cameras, which are used to estimate capsule deformation and 3-D strain fields during vertebral loading. (B) A fiber alignment map (shown in red lines), generated by polarized light imaging, shows collagen fiber alignment and its reorganization during facet loading, which alters the local biomechanical environment of any resident afferents in the ligament's collagen matrix. (C) Safranin O staining of the rat C6-7 facet, 6 weeks after facet joint distraction simulating physiological loading, shows the proteoglycan content of the facet joint cartilage (red); the close-up (inset) shows that facet cartilage does not exhibit signs of joint degeneration after nonpainful facet capsule loading.
after loading is removed.14,57 Interestingly, these strain magnitudes are consistent with those associated with pain27,52 and are also comparable to those generated during whiplash-like neck loading and those inducing microscopic injury of the capsular ligament in biomechanical testing.56,76,84,86 Together, these findings suggest that the local mechanical environment of the afferent fibers in the facet capsule likely plays an important role in modulating their responses to excessive joint stretch. This notion is further supported by in vitro work using a neuron-collagen gel construct system that mimics the capsule structure and innervation. Imposing bulk strains greater than 11% to a gel increases phosphorylation of extracellular-regulated kinase (ERK), an indicator of neuron activation, and causes collagen reorganization.115 This finding demonstrates that strains sufficiently large to initiate a neuronal response can also change the microstructure of the neuron’s environment. These in vitro results suggest that the strain thresholds for neuronal activation (ERK phosphorylation) and local tissue injury (collagen matrix reorganization) may be the same.115

In addition to immediate neuronal responses, facet capsular loading that induces behavioral hypersensitivity in the rat is also associated with many sustained modifications in the nociceptive signaling from the primary afferents that are evident in the DRG. Protein expression of the nociceptive neurotransmitter, substance P, is increased in the DRG after painful facet joint stretch by day 7, and that change is absent in nonpainful stretch.54 Capsular stretch-induced increases in DRG expression of the metabotropic glutamate receptor 5 (mGlur5) and its second messenger, protein kinase C-epsilon (PKCε), are strain dependent and are not evident until 7 days after the initial injury.17,27,103 The late upregulation of these molecules suggests that they may play a role in the later nociceptive pathways involved in injury-induced pain. Furthermore, because dorsal horn hyperexcitability and increased spontaneous activity develop between 6 and 24 hours after facet injury,19 it is unlikely that these neuromodulators play a role in the initial electrophysiology responses of afferents that parallel the onset of hypersensitivity. Because these neuromodulators (substance P, mGlur5, and PKCε) are involved in neuroplasticity and pain,13,100,103 their delayed elevation implies that the afferents undergo persistent activation and/or dysfunction after painful loading has occurred. Because axonal degeneration is known to take 7 days to develop,36,78 it may contribute to the late onset of modified nociceptive signaling.

A complex dysregulation of glutamatergic signaling in the spinal cord accompanies excessive facet stretch and drives nociception that causes pain. Painful facet injury modifies the spinal expression of a number of nociceptive molecules involved in excitatory glutamatergic signaling, including phosphorylated ERK, mGlur5, PKCε, and ionotropic glutamate receptor N-methyl-D-aspartate subunit.17,27,103 Expression of each of these nociceptive molecules is increased in the spinal cord along the same time course as sustained pain symptoms and spinal hyperexcitability.17,27,103 In addition to increases in expression of glutamate receptors, expression of glutamate transporters on astrocytes and neurons, which regulate the clearance of glutamate away from synapses, like glutamate aspartate transporter, glutamate transporter 1, and excitatory amino-acid carrier 1, is also altered in the spinal cord 1 week after painful facet stretch. While the astrocytic glutamate transporter (glutamate aspartate transporter) is upregulated 1 week after painful injury, both glutamate transporter 1 and excitatory amino-acid carrier 1, which are expressed on other cells, are downregulated, pointing to the widespread and complicated dysregulation of glutamate in pain from facet joint injury.17,27,103

Nociceptors innervating the facet joint transmit noxious stimuli from peripheral terminals to the spinal cord via action potential propagation. That peripheral inputs lead to increased neuronal firing is evidence of central sensitization (FIGURE 1).6 Increases in spontaneous and evoked neuronal firing in the spinal cord parallel the behavioral hypersensitivity that develops between 6 and 24 hours after excessive subfailure facet joint stretch in rats.19 A functional role of early afferent activity in pain transmission has been corroborated by a study in the rat that blocked afferent activity with a single joint injection of the anesthetic bupivacaine at early times after injury. Bupivacaine attenuated pain symptoms and prevented the development of spinal neuronal hypersensitivity when given immediately after injury, while the same administration at times even as early as 4 days later had no effect on modifying either response compared to the typical injury response.17 This narrow and early establishment of spinal modifications strongly supports a similarly narrow temporal window for intervention after a whiplash injury during which the onset of spinal mechanisms of sensitization can be prevented. The initial injury-induced hyperexcitability of dorsal horn neurons that develops by 24 hours after injury persists for at least 7 days in the rat.73,87,81

The sustained hyperexcitability of spinal neurons has been speculated to be maintained by structural and/or functional plasticity in the spinal cord.43 Indeed, structural plasticity is evident in the superficial dorsal horn, with approximately a 50% increase in the number of excitatory synapses that are present in the spinal cord, accompanied by a decrease in inhibitory synapses.19,48 This synaptic plasticity can potentiate the excitatory signaling that manifests as hyperalgesia and allodynia. These changes in synapse numbers are accompanied by both increases in the number of spinal cord neurons classified as nociceptive and decreases in the number of neurons classified as low-threshold mechanoreceptors.19,71 Clinically, these same phenotypic shifts can manifest as decreased pain thresholds to various stimuli.4 It is important to note that this phenotypic switch is only observed when...
the strain across the facet capsule exceeds physiological strains and produces pain, further supporting the notion that plastic changes in the spinal cord may also be severity dependent. Indeed, the decrease in inhibitory synapses observed 14 days after painful injury is also correlated with the severity of facet injury. Collectively, these studies provide evidence of spinal cord plasticity following painful facet injury that is severity dependent and can potentiate nociception of facet-mediated pain.

Facet joint trauma is a complex injury involving both mechanical insults as well as inflammatory cascades that stimulate neurons. A review of the cascades involved in inflammatory pain is beyond the scope of this commentary but can be found elsewhere. We do provide a brief review here of relevant findings following facet trauma as they may relate to whiplash. Like other chronic pain conditions, spinal astrocytes are activated for at least 14 days after painful facet stretch. Mechanical injury to the facet capsule also regulates the production of inflammatory mediators, including proinflammatory cytokines and neurotrophins, in the facet joint itself, as well as in the DRG. Because peripheral inflammation increases hyperexcitability and substance P in DRG neurons, along with pain production, recent studies have begun to elucidate the molecular mechanisms by which peripheral inflammation contributes to central sensitization in the context of facet-mediated pain. Recently, neurotrophins have been implicated both locally in the facet and to be more widespread in the CNS. Nerve growth factor (NGF) increases in the facet joint tissues as early as 1 day after a facet joint distraction that produces pain at that same time. Further, inhibiting NGF signaling also prevents the onset of pain and associated spinal neuron hyperexcitability when anti-NGF is given intra-articularly immediately after capsular stretch and before pain develops, suggesting a critical role of local NGF in initiating pain. Unlike NGF, expression of the neurotrophin brain-derived neurotrophic factor (BDNF) increases in both the DRG and spinal cord at a later time (day 7), with intrathecal administration of the BDNF-sequestering molecule trkB-Fc after facet injury partially reducing pain. Collectively, these NGF and BDNF studies not only reveal important novel pathways emerging as having critical roles in pain from whiplash injury, but also provide potential therapeutic targets for treating joint pain.

**The Challenges of Translating Basic Science to the Clinical Setting**

Although in vivo and in vitro models continue to inform about the pathophysiology of nociception in facet-mediated pain, there are several challenges in translating that work to the human condition and understanding injury risk, as well as in guiding clinical treatment. Among the major challenges of understanding the biomechanical mechanisms of whiplash pain is related to defining thresholds for joint injury, neuronal activation and dysfunction, and pain. Although basic science studies collectively have defined thresholds for neuronal activation and the induction of pain, those studies are based on work in vivo in the rat and/or goat, or even in artificial constructs simulating the ligament. Nonetheless, because a common, nondimensional biomechanical metric (strain) has been used across all of those studies, the findings are agnostic of species and/or scale, and it may therefore be possible to extend such findings to the human. The bigger challenges of understanding injury risk and predicting injury in humans are complicated by very complex and integrated systems at play in pain. For example, pre-existing physiological priming in the human could lower the threshold for neuronal activation and other responses. In fact, this has been shown in a rat model in which the typically physiologic facet loading is capable of producing pain if there is a prior exposure to chemical stimuli or prior loading.

Although biomechanical metrics like strain can be used to compare cadaveric, clinical, and animal studies that investigate mechanisms of whiplash, they do not fully capture the highly complicated anatomical and structural environment relevant to pain and injury. The highly variable structure of the facet capsular ligament, including its varied thickness, the variable length of the collagen fibers that comprise it, and the proportion of elastin fibers contributes to the heterogeneity of the facet capsule’s biomechanical response to loading. As such, the above metrics fail to fully capture relevant mechanical response that may be highly influential in driving the physiological response. The microstructural reorganization of the facet capsule’s extracellular matrix, composed mainly of collagen, is also heterogeneous, with more extensive collagen fibers in the posterior region of the capsule than in its lateral region. This regional variation in microstructure makes using any single injury metric as the gold standard challenging at best and inappropriate or inadequate at worst. Measurements of microstructural reorganization like collagen fiber realignment appear to be a better predictor of the onset of microstructural damage than strain measurements, which makes them a promising injury metric. However, acquiring such measurements remains technically difficult. Collagen fiber realignment, for example, is difficult to measure noninvasively or outside the laboratory, making it challenging to implement in studies of either global tissue responses or pain (in humans and/or animal models). Higher-resolution strain-field measurements combined with analyses that quantify unrecovered strain could provide promising approaches to identify the local biomechanics that initiate mechanosensation in afferents. Furthermore, although kinematics of the cervical spine and the facet joint under whiplash-like loading are well defined, those complex kinematics are difficult to apply in either an animal model or in isolated tissue tests, and the heterogeneity of the tissue could result in kinematics that may not reflect the clinical scenario. This challenge is exacerbated...
Clinical Commentary

Ariëns GA, van Mechelen W, Bongers PM, Bouter B, Braz JM, Nassar MA, Wood JN, Basbaum AI. Not only by the anatomical heterogeneity of the facet joint, but also by the scaling of biomechanical injury metrics to the in vivo environment.

While there is tremendous utility in relating thresholds for generating pathophysiological responses to the initiation of the cascades that regulate persistent pain, utilizing the emerging cellular and molecular schema for whiplash pain production has the greatest potential for informing and shaping clinical treatments. Indeed, work in animal models highlights potential points of modulation via altering or preventing aberrant neuronal activity,

and/or nociceptive signaling cascades,

Despite the effectiveness of such treatments in animal models, their translation to humans is challenging for many reasons. First, clinically, humans present with whiplash at varied times after the initial injury, and may or may not exhibit confounding predispositions and/or physiological states. As such, many of the treatments that are effective in vivo in basic science have effects only when administered in specific time frames after injury.

Because the clinical time between injury, treatment, and/or an intervention is not uniform, presentation of pain symptoms after whiplash-like injuries is highly variable, creating an inherent disconnect between preclinical findings and those at the clinic. In addition, the human condition of whiplash is accompanied by many psychosocial factors that are not present in animal models, including catastrophizing, fear avoidance, and confounding factors due to litigation, among other forms of psychosocial stress.

Although animal models are limited by not including these psychosocial factors, they also provide great utility in that physiological questions can be investigated without these confounding variables.

It is important also to recognize that there is a similar but equally important disconnect when moving from clinical studies to the laboratory. The pain systems that are most commonly assayed and reported for patients with whiplash are not easily translated to animal models. Certainly, spontaneous pain is commonly reported in patients with whiplash, and capturing the emotional components of pain is of the utmost importance in this syndrome. However, a reliable assessment of spontaneous pain in vivo in the laboratory remains the holy grail. Ultimately, establishing reliable assays and translatable studies, from both the laboratory and clinical realms, will help bridge activities elucidating molecular pathways of nociception and those in which treatment approaches are being trialed on patients with facet-mediated whiplash pain.

SUMMARY

Despite the challenges of meaningfully integrating the basic science mechanisms of pain from joint trauma with clinical management and diagnosis, the interdisciplinary efforts crossing silos of clinical, engineering, and physiological research have gone a long way to developing a model schema for understanding whiplash-related pain. In this commentary, we reviewed aspects of the complex anatomical, biomechanical, and physiological consequences of whiplash loading to the facet joint. In particular, basic science studies using facet loading were related to work with humans, either in the clinic or in the laboratory. Owing to the complexity of this problem, we focused on the macroscopic work defining tissue injury at the organ scale, with complementary work at the microscale, to understand the responses of collagen and neuronal cells. Managing the pathology of facet pain requires an even deeper understanding of the anatomical tissues, neuronal innervation and response in the facet joint, the susceptibility of that joint and its constituents to varying magnitudes of biomechanical loading, and the temporal physiological responses of mechanosensation. Most important, perhaps, is that each and every one of these signals and responses must be defined in the context of clinical pain symptoms. It is clear from the basic laboratory studies that the heterogeneous nature of the facet joint itself, and its cellular responses to painful loading, are primary contributors to the breadth of individual responses that are observed in patients with whiplash-related pain. Nevertheless, while a clear and consistent cellular/molecular schema for trauma-induced facet pain is emerging (FIGURE 1), fully understanding the nature of facet-mediated pain remains challenging.

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REFERENCES


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1. Sijia Zhang, Vahhab Zarei, Beth A. Winkelstein, Victor H. Barocas. 2017. Multiscale mechanics of the cervical facet capsular ligament, with particular emphasis on anomalous fiber realignment prior to tissue failure. Biomechanics and Modeling in Mechanobiology 41... [Crossref]