Intervertebral Disc Herniation: Pathophysiology and Emerging Therapies

19

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Contents

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19.1 Introduction

Approximately 2.6 % of the US population visits a physician for treatment of spinal disorders annually (Fraser 2009) with costs of $7.1 billion from lost work days alone (Ricci et al. 2006). "Herniation" of the intervertebral disc is one of the several spinal disorders that contribute to this very high incidence, with potential to cause significant pain, neurological deficit, and functional disability in affected individuals. Herniation presents as a protrusion or extrusion of discal tissue into the epidural cavity, resulting in nerve root impingement and disc tissue exposure (Fig. 19.1). Both mechanical compression and tissue exposure contribute to pain and disability associated with intervertebral disc herniation (Goupille et al. 1998; Mixter et al. 1934; Olmarker and Rydevik 1991). In areas innervated by the affected nerves, it is commonly seen as low back pain, radiating leg pain (i.e., radiculopathy or sciatica), muscle weakness, gait abnormality, muscle atrophy, asymmetric reflexes, or loss of function (Atlas et al. 2005; Frymoyer 1988; Hart et al. 1995). The incidence of sciatica related to intervertebral disc herniation peaks between the fourth and fifth decades of life and is most frequently associated with herniations between the L3 and S1 vertebral levels (Atlas et al. 2005; Awad and Moskovich 2006). The severity of herniation symptoms in the cervical or lumbar regions has been shown to relate to the size or nature of the herniated fragment, whether it is simply protruding into the neural cavity, extruded, or completely sequestered from the parent structure.

Intervertebral disc herniation may also occur in association with disc degeneration, wherein degenerated nucleus pulposus fragments migrate into previously established defects in the anulus fibrosus (Moore et al. 1996). A desiccated and fibrous nucleus pulposus is associated with loss of disc height and an increased axial disc bulge with compressive loading (Adams and Roughley 2006); the altered tissue can generate untoward stresses upon the anulus fibrosus leading to tissue fragment extrusion. Thus, while intervertebral disc degeneration is positively associated with disc herniation,

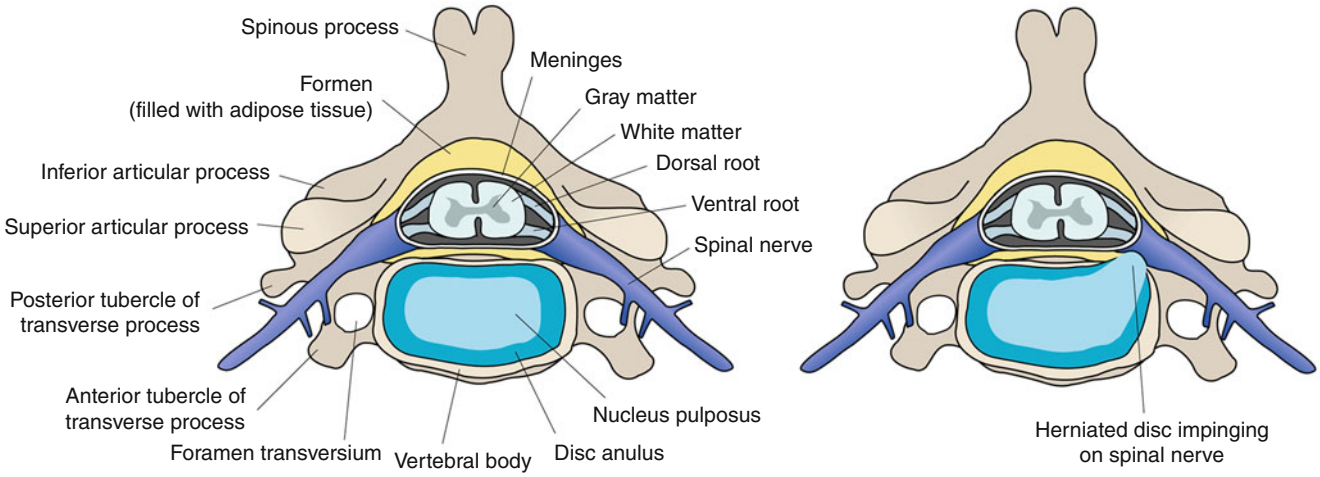


Fig. 19.1 Schema showing a cross section of the intervertebral disc and anatomy of the spinal cord and posterior vertebral processes. (*Left*) Normal anatomy showing labels identifying the intervertebral disc anulus fibrosus and nucleus pulposus, as well as the nerve roots which come together as spinal nerves as they exit through the intervertebral foramen. (*Right*) Schema of anatomic changes typical of a posterolateral intervertebral disc herniation, suggesting nerve root impingement (Used under CCL3.0, http://en.wikipedia.org/wiki/File:Cervical_vertebra_english.png)

it can be difficult to identify the specific contributions of biomechanical, environmental, or genetic factors. Once the tissue is protruded or herniated, there is evidence for increased angiogenesis, macrophage infiltration, and proteinase production in the tissue fragment that can contribute to its resorption over a period of months to years (Komori et al. 1996).

The factors listed above are also believed to play important roles in the etiology and pathophysiology of intervertebral disc herniation (Adams and Roughley 2006; Battie and Videman 2006). Mechanical loading of the lumbar spine in work-related loading conditions may be sufficient to cause disc herniation. Epidemiological studies further suggest a role for mechanical factors and nutrient transport in intervertebral disc herniation with higher incidences of herniation and sciatica associated with obesity, smoking, and heavy physical work (this topic is discussed in considerable detail in Chap. 9) (Battie et al. 2009; Bostman 1993; Heliovaara 1987a, b; Heliovaara et al. 1987a, b). Genetic predisposition to lumbar radiculopathy may also exist, with data suggesting that disc herniation may be associated with genetic mutations in the α2 and α3 chains of collagen IX or the regulatory cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6) (see Chap. 11).

For intervertebral disc herniation, the first treatment of choice is conservative, unless motor weakness or loss of function is a significant concern. Lifestyle modifications, in particular exercise and physical therapy, can provide symptomatic relief and reduce the need for operative treatment, although they are not generally considered to be disease-modifying therapies (Weinstein et al. 2006a, b). In addition, conventional pharmacological interventions are widely prescribed for sciatica including orally administered anti-inflammatory and opioid analgesics. While more invasive, epidural administration of anesthetics, such as bupivacaine, and/or corticosteroids, like methylprednisolone or triamcinolone, shows some efficacy in providing symptom relief, although again without evidence of disease modification (Buenaventura et al. 2009; Staal et al. 2008).

While nonsurgical care is the first treatment option (see Chap. 15), surgical intervertebral disc excision is the most frequently performed musculoskeletal procedure in the USA, affecting 0.3 % of the population with hospitalization costs of $9.5 billion (Fraser 2009; Ricci et al. 2006). The surgical approach for painful disc herniation is simply to remove the inflammatory material and to unload and decompress the adjacent neural structures (Loupasis et al. 1999). While frequently successful in providing relief, compression-relieving discectomy may not prevent recurrence of pain, prompting the need for additional surgeries, or in 20–60 % of patients, there may be repeat herniations (Weinstein et al. 2006a, b).

19.2 Pathophysiology and Pain of Intervertebral Disc Herniation

Both chemical and mechanical factors are widely believed to contribute to radicular pain subsequent to intervertebral disc herniation (Olmarker 2001). The herniated fragment may impinge upon the exiting spinal nerve and contribute to nerve root compression with many associated deleterious effects. The root consists of both anterior and posterior rootlets exiting from the spinal nerve that combine to form the dorsal and ventral nerve roots containing sensory and efferent fibers, respectively (Fig. 19.2). The roots come together in the region

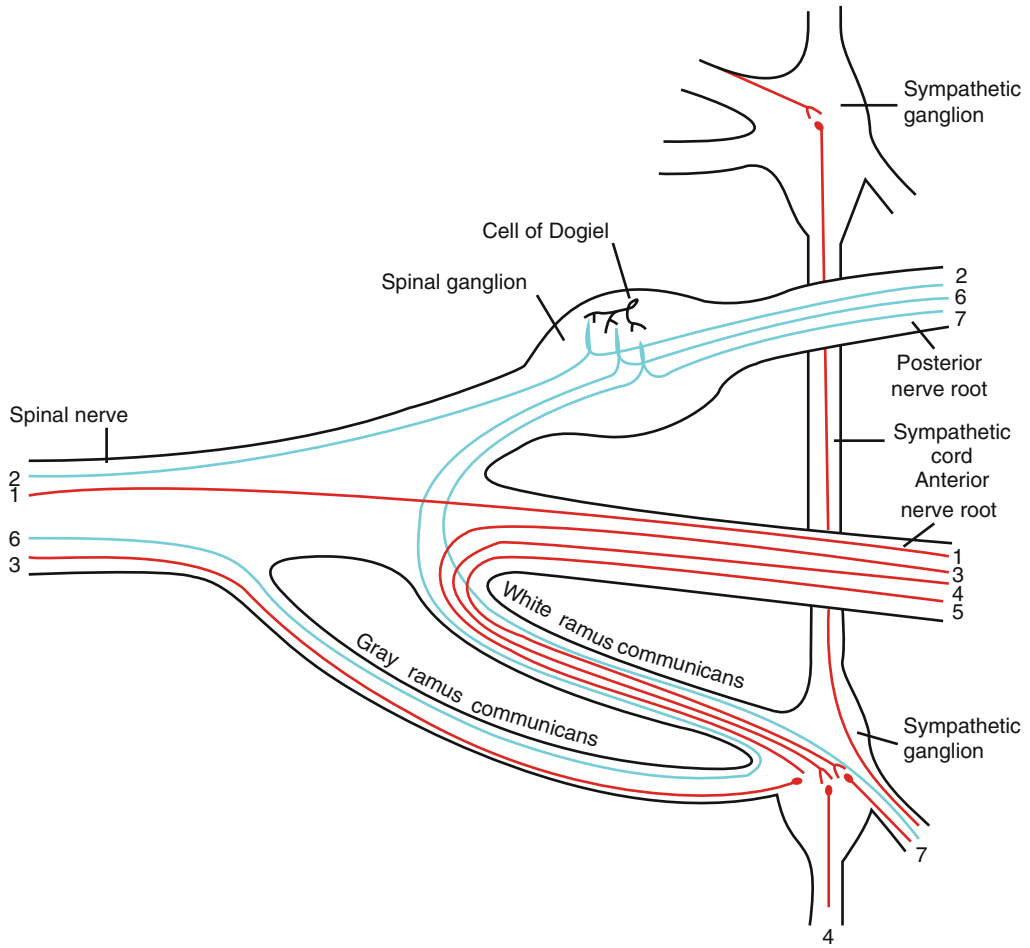


Fig. 19.2 Scheme showing structure of a typical spinal nerve and spinal ganglion. *1* Somatic efferent, *2* somatic afferent, *3, 4, 5* sympathetic efferent, *6, 7* sympathetic afferent (Figure 799 from Gray's Anatomy (Used under CCL3.0, http://en.wikipedia.org/wiki/File:Gray799.svg))

of the neural foramen and continue more distally into the periphery of the spinal nerve to innervate the structures outside of the spinal column. Unlike nerves, the nerve roots are not enclosed by a thick epineural sheath, and so they lack the mechanical resilience of their peripheral counterparts; hence, their structural anatomy places them at particular risk for injurious mechanical loading under intervertebral disc herniation. In addition, the cell bodies of peripheral nerves are housed in the dorsal root ganglion (DRG) and can respond to even slight compression with sustained neuronal activity and pain (Hanai et al. 1996; Hu and Xing 1998; Van Zundert et al. 2006). Intraoperative studies in patients with disc herniation and associated root impingement demonstrate decreases in the amplitude of compound muscle action potentials following electrical stimulation to the affected nerve root (Morishita et al. 2006; Takamori et al. 2011). This work provides direct support for the clinical observation that functional impairment is associated with disc herniation. Reproduction of pain generating straight-leg raises in patients undergoing surgery showed that the amplitude of the evoked action potentials decreased 41 % at as early as 1 min following positioning and decreased by 63 % after 3 min (Takamori et al. 2011). The change in evoked action potential continued to develop through the period of nerve root impingement, demonstrating that time-dependent electrophysiologic responses occur in the nerve root with compression. These changes in neuronal signaling probably contribute to radiculopathy symptoms. Together, the magnitude, duration, and rate of compression of the nerve root modulate both the extent of the local tissue damage and the degree and duration of the pain symptoms (Kobayashi et al. 2005b; Olmarker et al. 1989; Rothman et al. 2010; Rydevik et al. 1991; Winkelstein et al. 2002).

As indicated above, intervertebral disc herniation can contribute to a type of neuropathic pain that has, as its most common characteristic symptom, radicular pain or radiculopathy. Self-reported pain and disability scales, such as the visual analogue scale (VAS) or Oswestry Disability Index, are often used to provide measures of pain or functional loss associated with disc herniation. Clinically, the straight-leg raise test (or SLR) is considered the most sensitive approach for quantifying the

Table 19.1 Molecular mediators of radiculopathy identified in intervertebral disc tissues. Annotated findings in footnotes

Mediator	Notes	Citation
TNF-α	1–3,6	Weiler et al. (2005), Takahashi (1996), Demircan (2007), Ahn (2002), Le Maitre et al. (2007), Nygaard (2007)
ICAM-1	1	Doita et al. (1996)
Interleukin-1α	1,2	Le Maitre (2005), Takahashi (1996), Ahn (2002)
Interleukin-1β	1,3,7	Demircan (2007), Takahashi (1996), Le Maitre et al. (2005, 2007)
Interleukin-17	3	Shamji et al. (2010)
Interleukin-4	3,5	Shamji et al. (2010), Park (2002)
Interleukin-6	1,3,6	Demircan (2007), Takahashi (1996), Kang (1997), Burke et al. (2002), Shamji et al. (2010), Specchia (2002), Nygaard (2007)
Interleukin-8	1,2,4	Demircan (2007), Ahn (2002), Burke et al. (2002)
Interleukin-12	3,4	Shamji et al. (2010), Park (2002)
Interleukin-20	1	Huang (2008)
Interferon-γ	1,3,4	Demircan (2007), Shamji et al. (2010), Park (2002)
Leukotriene-B4		Demircan (2007), Nygaard (2007), Willburger (1994)
Thromboxane-B2	1,4,7	Demircan (2007), Nygaard (2007)
Phospholipase A	1	Saal (1990)
Prostaglandin E2	1,3	O'Donnell (1996), Kang (1997), Wilburger (1994)

1. Expression noted in degenerative and/or herniated IVD
2. Protein or mRNA expression revealed in herniated IVD alone
3. Herniated or degenerated IVD > non-degenerative or autopsy control
4. Uncontained > contained herniations or non-degenerative control
5. Expression in uncontained < contained herniations
6. No evidence of protein or mRNA expression in herniated discs
7. Little or no spontaneous expression detected in herniated IVD

degree of radicular pain originating in the lumbar region, as pain is more pronounced upon elevation of the leg (van der Windt et al. 2010). Similarly, positions that reproduce pain such as forward flexion, hyperextension, and slump are sometimes used to corroborate findings of radicular pain, although imaging is commonly needed to confirm the pain source is related to intervertebral disc herniation. In patients, physical tests of muscle weakness, impaired reflexes, and sensory deficits or hypersensitivity may also be used to detect impairment associated with radiculopathy. These diagnostic and quantitative assessments are relevant to animal models as no diagnostic biomarkers that span human to animal models have yet been developed for intervertebral disc herniation radiculopathy (Brisby et al. 2002; Gajendran et al. 2011; Tokunaga et al. 2010). Tests of hypersensitivity to non-noxious (allodynia) and noxious stimuli (hyperalgesia) serve as surrogate measures of sensory changes with disc herniation and can serve as indicators of neuropathic pain in both human subjects and animals. A heightened response to a light brush of the skin would be considered a sign of mechanical allodynia, while a heightened response to pinch would be considered a sign of mechanical hyperalgesia. Patients presenting with herniation may experience either or both mechanical or/and thermal allodynia, and these serve as important metrics of pain-related behaviors in animal models of intervertebral disc herniation.

Separate from nerve root compression, a herniated disc fragment may evoke an inflammatory and immune response near an affected root (Olmarker and Larsson 1998). Indeed, the herniated tissue fragment is a known generator of many inflammatory mediators and proinflammatory cytokines, such as IL-1α, IL-6, and TNF-α (Table 19.1). Elevated expression of these molecules may activate the immune system and upregulate the expression of proteinases important for fragment resorption; nerve root compression alone may also upregulate the expression of many of these same inflammatory mediators (Kobayashi et al. 2005b). Many mediators are known generators of pain, such that they have become therapeutic targets for new and emerging studies (reviewed at the end of this chapter).

19.3 Animal Models of Intervertebral Disc Herniation

To advance therapeutic options that can change disc herniation outcomes, it is of critical importance to understand the molecular mechanisms that regulate pain, muscle changes, and dysfunction. Animal models of herniation have been extensively studied for this purpose. These models fall into two categories: (1) models designed to mimic direct nerve root compression in a well-controlled manner using plungers, constriction, or graded compression (Hou et al. 2003; Kallakuri et al. 2005; Kawakami et al. 2003; Onda et al. 2005; Sekiguchi et al. 2009); (2) models designed to mimic chemical injury that can elicit an inflammatory response through the use of chemical irritants (Colburn et al. 1999; Hashizume et al. 2000a; Hubbard and Winkelstein 2005; Kajander et al. 1996; Kawakami et al. 1994a, b; Maves et al.

1993; Olmarker et al. 1993; Winkelstein and DeLeo 2004); or (3) direct application of nucleus pulposus tissue to the nerve root (Allen et al. 2011; Brisby et al. 2000; Cuellar et al. 2005; Kawakami et al. 1999; McCarron et al. 1987; Olmarker et al. 1997; Olmarker and Myers 1998; Otani et al. 1997; Sekiguchi et al. 2008; Shamji et al. 2009). All of these animal models mimic key features of painful radiculopathy such as limb allodynia or hyperalgesia. The most commonly reported measure of limb hypersensitivity in preclinical models of intervertebral disc herniation is mechanical allodynia, detected using von Frey microfilaments applied to the plantar region of an animal's paw (Fig. 19.5) (Colburn et al. 1999; Kallakuri et al. 2005; Kobayashi et al. 2005b; Shamji et al. 2009; Rothman et al. 2010; van der Windt et al. 2010). By measuring the frequency or response of withdrawal from a given filament, the sensitivity of a limb to non-noxious mechanical stimuli can be assessed. Mechanical hyperalgesia is also a measure of limb sensitivity and can be determined by recording the time spent grooming following a pinprick or assessing the mechanical pinch force required to initiate an animal response (Randall–Selitto device). These measures have some gross relationships to pain and serve as surrogate measures of underlying neuropathology with intervertebral disc herniation.

Pain or dysesthesia can also elicit changes in grooming, locomotion, or sensorimotor skills in animal models. Pain in disc herniation models has been identified by recording key features of animal behavior over a period of time, such as the frequency of head turns toward a respective limb, leg lifts, duration of spontaneous grooming activity on a given limb, and "wet-dog shakes" (see Chap. 16) (Nakamae et al. 2011; Nilsson et al. 2011; Olmarker 2008; Olmarker et al. 2002, 2003). Alternatively, quantitative measures of gait have been used to identify compensations and disabilities resulting from intervertebral disc herniation (Allen et al. 2011; Shamji et al. 2009), made easier by the recent introduction of digitized gait apparata including the CatWalk™, Treadscan™, and Digigait™ systems (Beare et al. 2009; Berryman et al. 2009; Gensel et al. 2006; Piesla et al. 2009; Vrinten and Hamers 2003). Tracking of spatial and temporal gait parameters, such as the geometric position of the limb and paw ground contact times, can be used to obtain measures such as stride length, step width, toe-out angle, stance times, gait symmetry (a measure of limping), and running velocity (Fig. 19.3). Dynamic data describe forces and moments that occur during a gait cycle and include measures such as ground reaction forces and moments (Crawley 2007; Whishaw and Kolb 2005). These parameters are standard analytical tools in the study of musculoskeletal injury and pathology and are more recently being used to objectively quantify pain-related behaviors and functional losses in animal models of disc herniation. The major models used to study mechanisms that contribute to symptoms of intervertebral disc herniation are reviewed here, followed by an overview of developments in the area of emerging nonsurgical therapies.

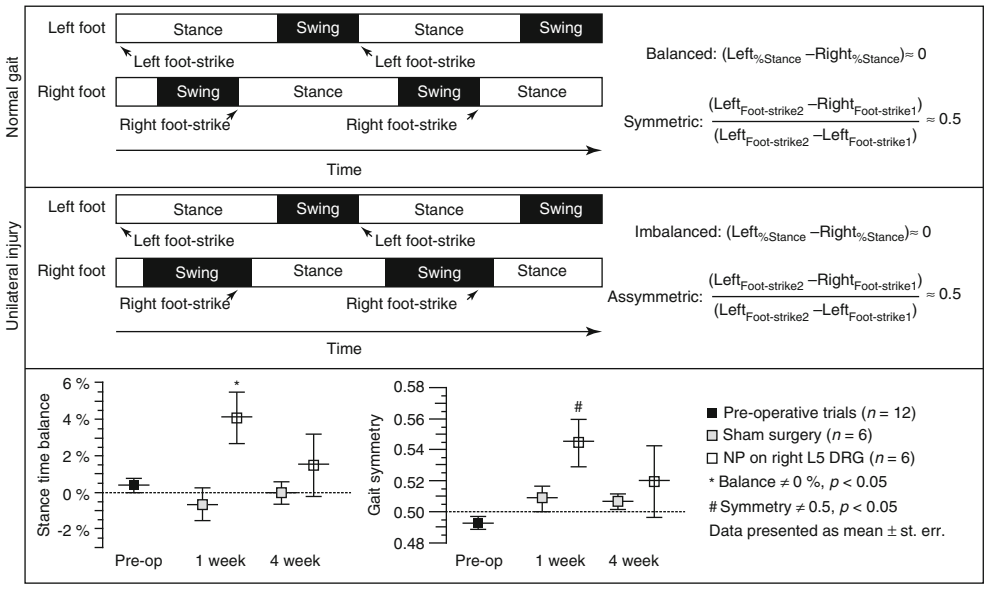


Fig. 19.3 Definitions of temporal parameters obtained from quantitative gait analysis. Rats freely ambulate across a clear gait chamber while digital video is acquired for determination of geometric positions of both hindpaws during each gait cycle. As shown, parameters of stance time, gait symmetry, as well as self-selected velocity, stance width, stride length, and more can be measured. (*Top*) Schema of a normal gait sequence wherein stance times are similar on the left and right hind limbs and a right foot-strike event occurs at the midpoint between two left foot-strike events. (*Middle*) For unilateral right limb injury, increased time is spent on the left limb and decreased time is spent on the right limb, as seen relative shifts in stance times. Also, the foot-strike sequence becomes syncopated in time, with the right limb foot strike occurring past the midway point of two left limb foot strikes. (*Bottom*) Data for stance time imbalance and gait symmetry of rats in a nucleus pulposus injury model of radiculopathy as compared to sham controls (Plotted from Hwang et al. (2012), used under CCL3.0)

Box 19.1 DRG and Neuronal Cell Culture

Intervertebral disc herniation can initiate cellular-level changes in the neurons and afferents in the dorsal root ganglion (DRG). Because many of these neuronal changes can contribute to central sensitization that induces sustained nociceptive responses in the spinal cord as well as pain, DRG culture studies are a useful proxy for investigating the pathophysiology of disc herniation. In particular, cell culture systems have the potential to recapitulate the cellular environment of primary afferents of the DRG via chemical and/or mechanical stimuli. In some cases, multi-compartment in vitro systems enable more complicated systems approaches to modeling synaptic connections, and integration of multi-electrode arrays in these setups also enables neuron-level assessments of function. In addition, culture preparations have been used to evaluate neuronal responses to challenges such as cytokines and other inflammatory mediators known to be involved in disc-mediated pain.

A variety of specialized techniques have been developed to isolate, maintain, and manipulate isolated neurons and intact DRGs from rodents. Briefly, immediately following perfusion with Krebs–Ringer bicarbonate buffer, laminectomies and facetectomies are performed to expose the DRG which is removed and immediately placed in Krebs buffer on ice. For isolation of intact neurons, the DRG is digested in collagenase under sterile conditions in Hank's Balanced Salt Solution, trypsinized, and dissociated by trituration. After trypsin inactivation, cells are resuspended in Dulbecco's Modified Eagle Medium (DMEM) supplemented with fetal bovine serum, growth factors, and antibiotics. Intact rodent DRGs may also be incubated with organ culture medium (DMEM and serum that is supplemented with glucose and nerve growth factor). Isolated neurons can be cultured on a variety of different substrates and exhibit varied responses depending on the substrate stiffness. Typically, cells are plated with culture media on glass-bottom dishes coated with poly-D-lysine in borate buffer and laminin in borate buffer. It is possible to phenotype DRG cultures to identify afferent populations using immunohistochemistry techniques to identify A fibers (by positive NF200 labeling), C fibers (negative for NF200 labeling), and also peptidergic (substance P positive) and non-peptidergic fibers (IB4 positive).

Although these culture techniques have been widespread in the neuroscience community for quite some time, they are becoming more common for understanding disc-mediated pain since they can provide a cellular-level characterization of neuronal responses to relevant stimuli related to disc herniation. They enable dose–response studies and real-time functional assays, as well as provide an exciting platform for screening potential therapeutics.

19.3.1 Mechanical Factors in Intervertebral Disc Herniation

Nerve root compression in association with disc herniation can result from acute insult to the axonal, connective, and vascular tissues of the nerve root and initiate a cascade of related and integrated neuronal, inflammatory, and degenerative changes (Kobayashi et al. 2004b; Rydevik et al. 1984, 1994; Winkelstein et al. 2002). From this perspective, mechanical injury and inflammatory injury are not unique, nor unlinked, events. Nerve root compression following acute mechanical loading can induce long-term nerve root pathophysiology, such as edema, inflammation, and thickening of connective tissues (Beck et al. 2010; Jancalek and Dubovy 2007; Kobayashi et al. 2004b; Mosconi and Kruger 1996), as well as the development of evoked pain via modified communication with the spinal cord. Following mechanical trauma and compression, injured axons exhibit axonal swelling, loss of cytoskeleton proteins, separation and disorganization of the myelin sheath, loss of axonal transport, Wallerian degeneration, and a decrease in axon packing density (Guertin et al. 2005; Jancalek and Dubovy 2007; Kobayashi et al. 2004a, b, 2005a, b, c, d; Mosconi and Kruger 1996; Myers et al. 1993). Like functional changes in neurons during and after compression, degenerative changes in axons develop at later times and are also dependent on the magnitude of the compression (Hubbard et al. 2008b; Kobayashi et al. 2005b; Nicholson et al. 2011).

Cells that respond to injury include microglia (resident macrophages in the central nervous system) and astrocytes. These cells have many roles in both the peripheral and central nervous systems, including the maintenance of homeostasis at neuronal synapses. Both types of glial cells respond to injury by changing their morphology, proliferating, upregulating cell surface markers, and releasing several inflammatory mediators (Cao and Zhang 2008; DeLeo et al. 2004; Saab et al. 2008; Suter et al. 2007). A peripheral stimulus by some neurotransmitters/neuromodulators (e.g., excitatory amino acids, substance P, ATP) (Cao and Zhang 2008; Marriott 2004) can activate early release of proinflammatory cytokines as well as nitric oxide, prostaglandins, and nerve growth factor (DeLeo et al. 2004; Inoue 2006). These mediators, in turn, induce an exaggerated release of neurotransmitters

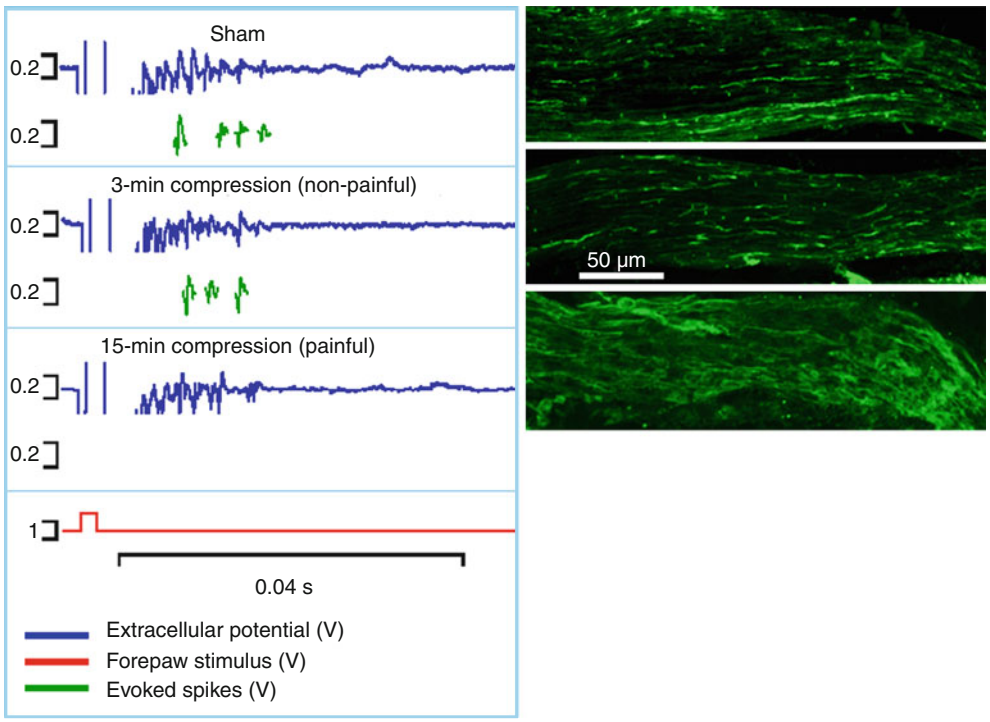
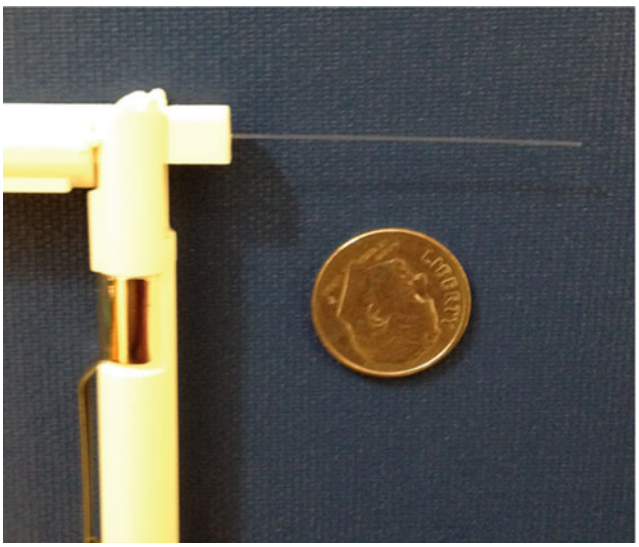


Fig. 19.4 Both the spinal extracellular potential (*blue trace*) and number of spikes evoked by electrical stimulus (*green traces*) generated following a nerve root compression are modified by the duration of the applied compression. The longer duration (15 min) compression that produces pain symptoms also causes an abolishment of evoked responses and decrease in EC response. In addition, that loading scenario also produces axonal swelling in the unmyelinated nerve fibers of the root that is absent in the 3-min (non-painful) compression

from presynaptic neurons, sensitize the postsynaptic membrane, activate neighboring astrocytes, and enhance microglial activity (DeLeo et al. 2004; Inoue 2006). This positive feedback sustains the release of pain mediators, facilitating the development of neuronal hypersensitivity and can lead to the persistent pain that is often associated with a herniated disc or inflamed nerve root. Following such neural insults, spinal glial cells become activated and modulate other immunologic changes via cytokine and growth factor production, leading to persistent pain (DeLeo and Yezierski 2001; Hashizume et al. 2000a; Obata et al. 2004; Winkelstein et al. 2001a). In particular, greater nerve root compression leads to increased activation of spinal astrocytes that is apparent as early as 1 day and is sustained in parallel with persistent symptoms of mechanical allodynia (Rothman and Winkelstein 2007). These observations suggest that spinal astrocytes may directly respond to the changes in the dorsal horn that are induced by damaged primary afferents (Hogan 2007; Sapunar et al. 2005) (Fig. 19.4).

Severe axonal injury can also induce Wallerian degeneration of the axonal process distal to the cell body (Stoll and Jander 1999; Stoll and Muller 1999). For the central axons of primary afferents, which make up the dorsal nerve root, Wallerian degeneration can occur proximal to the site of injury (Hubbard and Winkelstein 2008; Kobayashi et al. 2008). Axonal degeneration, marked by neurofilament degradation and loss of axonal integrity, is evident as early as 15 min after trauma, but is more commonly present at time points in the order of weeks (Kobayashi et al. 2008; Ramer et al. 2004). The extent of degeneration is modulated by the mechanics of the insult and is associated with persistent pain and hypersensitivity after a compression to the nerve root (Dyck et al. 1990; Hubbard et al. 2008a, b; Kobayashi et al. 2008; Nicholson et al. 2011) (Fig. 19.5). Disruption to the axonal structure has been found to be more pronounced for greater loads applied for longer durations (Dyck et al. 1990; Hubbard et al. 2008a; Kobayashi et al. 2005a, 2008; Nicholson et al. 2011). Further, the extent of damage and Wallerian degeneration of the axons in the compressed nerve root is directly related to the development of persistent hypersensitivity (Hubbard et al. 2008a, b; Hubbard and Winkelstein 2008).

The severity of nerve root injury and the intensity of pain after nerve root injury inflammation strongly relate to neuropeptide depletion in the DRG and spinal cord together with axonal degeneration (Hubbard et al. 2008a, b; Rothman et al. 2005). For example, persistent allodynia, due to higher magnitudes of dorsal nerve root compression, is associated with greater sensitivity at 1 week or later (Hubbard et al. 2008a, b). This is accompanied by a corresponding depletion of the nociceptive neuropeptide, substance P, in the DRG that similarly varies with the magnitude of the initiating compressive load (Hubbard et al. 2008b; Kobayashi et al. 2005b). Spinal expression of another potent neuropeptide for regulating pain, calcitonin gene-related peptide (CGRP), also decreases with increased painful loading to the nerve root (Hubbard et al. 2008a, b). Together with the



Example of 4 g von Frey filament

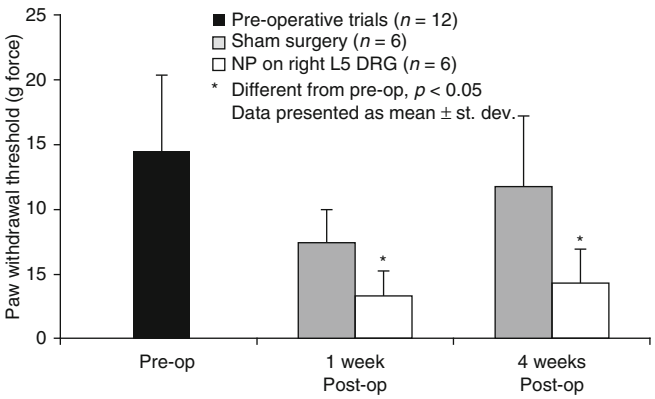


Fig. 19.5 Apparata and typical results for measuring mechanical allodynia in a rodent model of radiculopathy. (*Left*) von Frey filaments are logarithmically graded (e.g., 4g as shown) by buckling load upon compressive application. (*Right*) When filaments of varying strengths are applied to the hindpaw of a rat following placement of nucleus pulposus tissue upon the lumbar dorsal root ganglion (*DRG*), paw withdrawal is recorded over multiple trials and filaments. Data for paw withdrawal threshold of rats in an NP injury model of radiculopathy as compared to sham controls. Data show that nucleus pulposus placement upon a naïve DRG induces a paw withdrawal at lower filament strength, indicative of a persistent sensitivity to non-noxious stimuli (mechanical allodynia) (Plotted from Hwang et al. (2012), used under CCL3.0)

effects of neural trauma described above, these mechanically deleterious events can dramatically contribute to reduced transport of neuropeptides and neurotrophic factors from neurons, where these factors are synthesized, to their release from the presynaptic terminals in the spinal cord.

In animal models, the magnitude, duration, and rate of the nerve root compression have been shown to modulate the extent of the local tissue damage to the root and the degree and duration of the pain-related behaviors (Kobayashi et al. 2005a; Olmarker et al. 1989; Rothman et al. 2010; Rydevik et al. 1991; Winkelstein et al. 2002). In rodent models of nerve root compression, elevated magnitudes of compression increased the levels of mechanical allodynia and reduced axonal transport in the compressed root (Kobayashi et al. 2005a; Winkelstein et al. 2002). Although animal models of nerve root compression have shown sustained mechanical hypersensitivity in the affected limb (Colburn et al. 1999; Hashizume et al. 2000a; Kobayashi et al. 2005a; Winkelstein and DeLeo 2004; Winkelstein et al. 2002), mechanical hypersensitivity can also be produced when the nerve root is compressed for times as short as 2 s (Sekiguchi et al. 2003, 2009). Moreover, lumbar nerve root compression produces an immediate change in evoked signal conduction along the fibers of the compressed root (Fumihiko et al. 1996; Morishita et al. 2006; Pedowitz et al. 1992; Rydevik et al. 1991; Takahashi et al. 2003). Both compression rate and magnitude contribute to edema production in the nerve root, such that the magnitude of pressure required to produce edema decreases for higher loading rates (Hubbard et al. 2008b; Hubbard and Winkelstein 2008; Nicholson et al. 2011, 2012; Olmarker et al. 1989; Rothman et al. 2010; Rydevik et al. 1991). Moreover, specific loading parameters, such as magnitude and duration, likely play a role in modulating electrophysiologic responses. Animal models of nerve root compression in the cauda equina demonstrate that evoked neuronal signaling is altered during and after compression (Fumihiko et al. 1996; Garfin et al. 1990; Pedowitz et al. 1992; Rydevik et al. 1991) and decreases in the amplitude of electrically evoked compound nerve action potentials due to cauda equina compression may persist after removal of the compressive force (Pedowitz et al. 1992; Rydevik et al. 1991). These changes are corroborated by measurements in human subjects with intervertebral disc herniation that similarly show changes in evoked nerve action potentials upon straight-leg raise.

The results of studies of mechanically compressed nerve roots together with the widespread molecular changes can be integrated into a generalized schema. As early as 1 h following even a transient nerve root compression that is sufficient to produce persistent behavioral sensitivity, inflammatory cytokines, IL-6 and TNF-α, and mRNA expression levels are elevated in the ipsilateral DRG and also in the spinal cord (Rothman et al. 2009b). Within 1 day of that event, behavioral sensitivity develops along with hallmarks of spinal inflammation, including activation and proliferation of microglia (Rothman et al. 2009a). By 7 days after injury, axons of the injured nerve root show signs of degeneration, and the spinal inflammation becomes even more pronounced, and both astrocytes and microglia become activated (Hubbard and Winkelstein 2005, 2008). These changes together with the decrease in neuropeptides in the spinal cord at this same time point (Hubbard et al. 2008b) may lead to alterations in neuronal signaling in the spinal cord following a painful injury.

19.3.2 Role of Chemical and Inflammatory Mediators in Disc Herniation

As mentioned above, contributing to a cascade of chemical injuries at the affected nerve are elevated levels of inflammatory mediators, infiltration of macrophages, and activation of glial cells. To further examine these effects, animal models have been developed that mimic features of both inflammation and immune system function in intervertebral disc herniation. Both behavioral hypersensitivity and widespread immune responses are produced when chromic gut suture pieces are placed in contact with the nerve root without any mechanical perturbation (Colburn et al. 1999; Hashizume et al. 2000a; Hou et al. 2003; Hubbard and Winkelstein 2005; Kajander et al. 1996; Kawakami et al. 1994a, b; Maves et al. 1993; Murata et al. 2004a, b; Olmarker et al. 1993; Rothman and Winkelstein 2007; Rutkowski et al. 2002; Winkelstein and DeLeo 2004). Gut suture ligation simultaneously compresses the nerve root by ligation, while the chromic salts and pyrogallol in the suture serve as irritants (Colburn et al. 1999; Hashizume et al. 2000a; Kajander et al. 1996; Kawakami et al. 1994a, b; Maves et al. 1993; Robinson and Meert 2005; Winkelstein and DeLeo 2004; Xu et al. 1996). A consistent response to the chromic gut suture by the nerve root damage is the induction of thermal hyperalgesia (decreased latency to withdraw from thermal stimuli) that is transient and dose dependent; this form of hyperalgesia is not consistently present in intervertebral disc herniation models that mimic the compressive stimuli alone (Maves et al. 1993; Yamamoto and Nozaki-Taguchi 1995). The mechanisms governing the neuronal responses to chromic gut salts appear to be related to early immune activation characterized by Schwann cell proliferation, macrophage infiltration, and microglial activation. Along with these changes are molecular events including a depleted neuropeptide expression and an early expression of cell adhesion molecules such as ICAM-1 and PECAM. These adhesion molecules would serve to promote recruitment of circulating monocytes to the injured nerve root (Chang and Winkelstein 2011; Hashizume et al. 2000a; Rothman et al. 2010; Rutkowski et al. 2002; Xu et al. 1996; Yamamoto and Nozaki-Taguchi 1995). These studies indicate that, despite similarities in sensitivity to chromic gut suture and mechanical compression, differences in the pattern of hypersensitivity and molecular changes may reflect only limited injury etiologies. Nonetheless, use of chromic gut sutures as a chemical injury model for nerve root damage is popular for evaluating treatments that can interfere in the perception of disc herniation-related pain.

Soft tissues of the disc are believed to be immune privileged, in that the internal structures of the intervertebral disc do not come into contact with the systemic circulation under normal conditions and express the Fas ligand that can promote an autoimmune response. With degeneration and damage, the internal structures of the intervertebral disc can come in contact with adjacent tissues, producing an immune response that is the subject of extensive investigation. Intervertebral disc tissues contain high levels of CD68+ immunoreactive macrophages, as well as lesser quantities of T and B lymphocytes (Doita et al. 1996;

Box 19.2 Historical Information on Sciatica

What we currently understand as "sciatica" was originally considered an "evil display of demon magic" by the earliest civilizations to provide written record (Sigerist 1934). The Greeks of fifth century BC provide documentation of early attempts at treating the sudden shots of pain that were common to the spine–hip–joint complex. In Hippocratic times, corrective traction was often undertaken, with more conservative treatment that included massage, heat, dietary alterations, bed rest, and music "to pipe away pain." A particular Roman physician of the fourth century AD, Caelius Aurelianus, is noted for providing some attempt at explaining the etiopathogenesis and anatomic origins of sciatica (Drabkin ed 1950). Caelius Aurelianus believed that a sciatic attack could be caused by a sudden jerk or movement during exercise, lifting a heavy object, a sudden shock, or fall and that this presentation was most common for middle-aged persons. Surprisingly, these early Roman observations are all consistent with our present-day understanding. Further, Caelius Aurelianus believed that sciatica could be caused by a "deep-seated congelation," referring to a cutting off of squeezing of nervous tissue. In the day of Caelius Aurelianus, patients afflicted with sciatica may have been treated with a mixture of "sweet marjoram, rosemary leaf, wine, and olive oil," as well as bed rest, massage, heat, and passive range-of-motion exercises. If met with failure, a Roman may have undergone treatment with leeches, hot coals, skin hooks, and bloodletting.

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Source: Adapted from Karampelas et al. Neurosurgery Focus V16: pp. 1–4, 2004

Box 19.3 Glossary of Terms

Schober index Schober index measures a patient's ability to flex the lumbar region of his or her back. In a normal standing posture, a mark is made 5 cm above and 10 cm below the iliac spine. The patient then bends to full flexion, and the distance between the two marks is measured. A distance above 20 cm in flexion is considered normal, where distances below 20 cm during flexion suggest a limited range of motion.

Oswestry Disability Index The Oswestry Disability Index is a validated questionnaire commonly used to evaluate the principal conditions associated with spinal disorders. The Oswestry Disability Index evaluates self-reports of pain intensity, emotional well-being, and ability to perform common tasks.

Visual analogue scale (VAS) Visual analogue scales are commonly used in questionnaires and surveys as ranking statistics, where subjective semiquantitative ranks are used to assess a patient's relative improvement or decline.

Radiculopathy A medical condition where one or more nerves do not function properly resulting in radicular pain, numbness, and weakness and dysfunction.

Sciatica A sharp pain sensation or series of painful sensations affecting the back, hip, or leg. Sciatica can result from compression or inflammation of the spinal nerve root in the lower back and is often described as "shooting pain" down the leg.

N-Methyl-D-aspartic acid (NMDA) receptor NMDA receptors are ionotropic glutamate receptors that help to control synaptic plasticity and regulate nociception. NMDA receptors have been identified as key regulators of peripheral and central sensitization in lumbar radiculopathy.

Allodynia Allodynia is the sensation of pain from stimuli that would not typically cause pain. Mechanical allodynia, a heightened sensitivity to light touch, and cold allodynia, a heightened sensitivity to cold, have been observed in several models of lumbar radiculopathy.

Hyperalgesia Hyperalgesia is a prolonged or exaggerated pain response to stimuli that typically would cause pain. Thermal hyperalgesia, a heightened sensitivity to heat, and mechanical hyperalgesia, a heightened sensitivity to a pinch or pinprick, have been observed in several models of lumbar radiculopathy.

Dysesthesia Dysesthesia is a sensation described as unpleasant or abnormal, but not considered painful. Dysesthesia is among the symptoms reported from neuropathies and is often associated with descriptions of limb weakness and numbness.

Ground reaction force Ground reaction forces occur as a limb contacts the ground during motion and are typically described by three ground reaction force components. Vertical ground reaction forces help to support body weight during motion. Braking and propulsive ground reaction forces occur in the direction of travel and help to propel the body forward during locomotion. Mediolateral ground reaction forces are directed toward an animal's or person's midline and help to stabilize and balance the body during locomotion.

Wet-dog shake A characteristic shaking motion resembling a wet dog shaking out its coat. The frequency of wet-dog shake motions increases in rat models of lumbar radiculopathy.

Freemont et al. 2002; Gronblad et al. 1994; Roberts et al. 2006; Shamji et al. 2010). In addition, the disc tissues secrete numerous proinflammatory cytokines and inflammatory mediators, such as interleukin-1α (IL-1α), interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α); these cytokines may be produced by primary disc cells or by infiltrating monocytes (Bachmeier et al. 2009; Burke et al. 2002; Le Maitre et al. 2007; Murata et al. 2004a; Saal 1995; Shamji et al. 2010; Weiler et al. 2005, 2011) (Table 19.1). Numerous studies have documented the molecular effects of the herniated discal tissues (Mulleman et al. 2006a, b). Models used for these studies have included harvest of tail nucleus pulposus tissue for placement at a lumbar nerve root or cauda equina (Allen et al. 2011; Aoki et al. 2002; Brisby et al. 2000; Cuellar et al. 2005; Kawakami et al. 1999; Shamji et al. 2009; Skouen et al. 1999; Yabuki et al. 1998) or lumbar disc puncture to promote nucleus pulposus herniation (Olmarker et al. 1998; Olmarker and Myers 1998; Otani et al. 1997). Physiological changes noted in these models include reduced nerve conduction velocities, lowered endoneurial pressure for dorsal horn or sensory neurons, and elevated nitric oxide synthase activity in spinal nerve roots at 1–4 weeks following exposure to discal tissues. In addition, there is increased expression of neurotrophins, IL-1β, TNF-α, phospholipase-1, and/or nitric oxide synthase in the applied nucleus pulposus tissues or in cell bodies and intercellular domains around the DRG (Kallakuri et al. 2005; Kawakami et al. 1999; Murata et al. 2004a; Onda et al. 2002). Disc-associated cytokines (IL-1β, TNF-α, IFN-γ) applied directly to nerve roots, as opposed to cytokines secreted by nucleus fragments, have also been shown to induce electrophysiological changes, consistent with a heightened sensitivity (Ozaktay et al. 2002; 2006). It is likely that these cytokines bind to receptors for TNF-α and IL-1β on the sensory neurons (Binshtok et al. 2008; Verri et al. 2006). While these findings clearly indicate a

role for inflammation and inflammatory mediators in regulating neuronal sensitivity in intervertebral disc herniation, it must be noted that many changes in the nucleus pulposus-induced or chemical injury models of radiculopathy overlap with those reported for direct compression neuropathy.

As with direct nerve root compression or chromic gut suture exposure, application of nucleus pulposus tissue to a naïve nerve root induces limb hypersensitivity that is largely characterized by a mechanical allodynia (Hou et al. 2003; Mulleman et al. 2006a, b) (Fig. 19.5). Many studies of nucleus pulposus-induced radiculopathy following disc puncture to induce nucleus herniation or placement of nucleus pulposus tissue upon the nerve root report evidence of allodynia as early as 2 days that may persist out to 3 weeks (Kawakami et al. 1999; Obata et al. 2002). Early studies also report functional changes following nucleus pulposus-induced radiculopathy, including altered footprints and visual evidence of limping, paw lift, or rotation of the head (Olmarker et al. 1998, 2002). With the use of quantitative gait analysis, our laboratories have further demonstrated gait asymmetries between ipsi- and contralateral hind limbs out to 3 or 4 weeks postoperatively, indicative of limping (Shamji et al. 2009) (Fig 19.3). Static and dynamic gait analyses indicate that animals with radiculopathy bear less weight on their affected hindpaw in both stance and during locomotion (Allen et al. 2012).

The findings discussed above suggest that radiculopathy induced by DRG exposure to nucleus pulposus tissue, as a model of intervertebral disc herniation, can repeatedly mimic key characteristics of prolonged pain sensitivity in the human patient (Allen et al. 2011; Shamji et al. 2009). The finding of persistence of sensitivity supports the notion that the molecular responses of an inflamed disc may influence sensory changes during intervertebral disc herniation. The persistent sensitivity changes, extending beyond fragment removal or resorption, imply that the widespread responses imitated in the CNS and even systemically are not ameliorated. Once initiated, the neuroimmune cascade involves activation of many nonneuronal cells in the peripheral tissues (DeLeo and Yezierski 2001; Julius and Basbaum 2001; Moalem and Tracey 2006). These resident cells, including mast and Schwann cells, release mediators such as histamine, prostaglandins, cytokines, and chemokines that also lead to the recruitment of other infiltrating immune cells (e.g., neutrophils, macrophages, lymphocytes) (DeLeo and Yezierski 2001; Moalem and Tracey 2006; Verri et al. 2006). Proinflammatory cytokines also trigger the release of many other inflammatory mediators that can sensitize nociceptors, further maintaining neuronal excitability and sensitization and leading to dysfunction and pain (Moalem and Tracey 2006; Verri et al. 2006). Nonetheless, the persistence of pain observed in some human subjects following intervertebral disc herniation that may continue for months and even years has not been replicated in these animal models, where mechanical allodynia or thermal hyperalgesia can recover to control or preoperative values at later times after surgery. Additional studies of CNS sensitization in human and animal models of disc herniation are needed to better understand the role of these important pathway changes in the pathogenesis of disc pain.

Taken together, with knowledge gained from direct nerve root compression studies, it becomes clear that many of the sensitization and functional changes associated with disc herniation may reflect contributions from both compressive trauma as well as inflammatory agents in the disc. While somewhat intuitive, the more severe nerve root injuries (with greater degrees of tissue impingement) produce more pain-associated behavioral sensitivity than those injuries with less tissue compression (Hubbard et al. 2008b; Hubbard and Winkelstein 2005; Winkelstein et al. 2001b, 2002). This graded relationship has been shown to hold true regardless of the absence or presence of molecular challenges (Winkelstein and DeLeo 2004). Indeed, evidence that the duration of the mechanical trauma modulates several different pain pathways strongly supports the concept that a more permanent mechanical insult would produce a similar or even more robust deleterious clinical effect. Based on these understandings, clinical interventions, and specifically nonsurgical therapies, are focused on alleviating the persistent sensitivity that is associated with a transient or more chronic compressive trauma to the nerve root and the associated inflammatory events. This topic is briefly covered in the next section on emerging pharmacological approaches to treat intervertebral disc herniation-associated radiculopathy.

19.4 Emerging Therapies for Intervertebral Disc-Associated Radiculopathy

As mentioned in Sect. 19.1, in the absence of motor weakness or related loss of function, conservative care is the preferred treatment for a patient presenting with pain and symptoms of radiculopathy secondary to an intervertebral disc herniation. Conservative care most frequently involves lifestyle modifications as well as orally administered nonsteroidals or opioid analgesics. Commonly prescribed selective or nonselective nonsteroidal drugs include ibuprofen, indomethacin, diclofenac, piroxicam, diflunisal, and celecoxib, few of which have demonstrated significant effects on radicular pain associated with disc herniation (Chou and Huffman 2007) (also see Chap. 15). In animal models, indomethacin, ibuprofen, diclofenac, and celecoxib have been shown to reverse allodynia following peripheral or nerve root compression and may work by lowering prostaglandins and inhibiting the resulting decreases in nerve conduction velocity and decreased intraneural blood flow (see Table 19.2). Epidural administration of anesthetics such as bupivacaine and/or corticosteroids, including methylprednisolone, is also widely used for treatment of symptoms with

Table 19.2 Summary of compounds under investigation for treatment of IVD herniation-associated radiculopathy

Agent	Route	Model description	Reference	Observations
Anti-inflammatories				
Indomethacin	Oral	Canine lumbar nerve injury	Arai et al. (2004)	Reversed changes in intraneural blood flow and nerve conduction
Ketoprofen	Systemic (i.m.)	Porcine nerve root constriction or NP tissue placement	Cornefjord et al. (2001)	Partly reversed decreased nerve conduction velocity in constriction but not NP exposure
Diclofenac	Systemic (i.m.)	Porcine nerve root constriction or NP tissue placement	Cornefjord et al. (2001)	Partly reversed decreased nerve conduction velocity
Ibuprofen	Oral	Rat sciatic nerve compression injury	Schafers et al. (2004)	Reduced mechanical allodynia at short times after injury, reduced PGE2 levels in nerve and DRG
COX-2 inhibitor celecoxib	Oral	Rat sciatic nerve compression injury	Schafers et al. (2004)	Reduced mechanical allodynia at short times after injury, reduced PGE2 levels in nerve
NO synthase inhibitor (L-NAME)	Intrathecal	Rat lumbar DRG compression injury	Ding et al. (2010)	Some reversal of thermal hyperalgesia, decreased nitrite in DRG
Prostaglandin E2 receptor antagonist (EP1-RA)	Oral	Rat exposure of lumbar DRG to NP	Sekiguchi et al. (2011)	Reduced mechanical allodynia, attenuated increased activating transcription factor-3 (ATF3) immunoreactive positive cells induced by NP
Thromboxane A2 synthetase inhibitor	Epidural	Rat exposure of lumbar DRG to NP	Kawakami et al. (2001)	Reduced mechanical allodynia
Leukotriene B4 receptor antagonist (LTB4 receptor antagonist)	Epidural	Rat exposure of lumbar DRG to NP	Kawakami et al. (2001)	Reduced mechanical allodynia
COX-2 antibody	Intrathecal	Rat exposure of lumbar DRG to NP	Ohtori et al. (2004)	Reduced mechanical allodynia
Neuronal receptor modifiers				
NMDA receptor antagonist, MK-801	Intraspinal or systemic (i.p.)	Rat spinal nerve or sciatic nerve constriction injury	Chaplan et al. (1997), Uceyler et al. (2008)	Reversed molecular changes in CNS, partly reversed motor changes
Gabapentin	Systemic i.p. or local (perineural) delivery	Rat sciatic nerve or lumbar nerve root constriction injury	Abe et al. (2002), Zanella et al. (2008)	Some reversal of mechanical allodynia
Sarpogrelate hydrochloride (5-HT2A receptor antagonist: 5-HTRA)	Systemic	Canine or rat DRG exposure to NP	Sekiguchi et al. (2008), Hashizume et al. (2007)	Decreased blood vessel diameter and increased blood flow in nerve roots inflamed by NP application, partly reversed mechanical allodynia
Cell cycle modifiers				
Minocycline	Systemic i.v. and prophylactic delivery	Rat cervical nerve root compression and chromic gut exposure	Rothman et al. (2009b)	Some reversal of mechanical allodynia, no changes in spinal microglial proliferation
Methotrexate	Intrathecal or local	Rat lumbar DRG constriction with chromic gut	Hashizume et al. (2000b)	Reduced allodynia, no changes in spinal glial activation
Pathway inhibitors				
Ruthenium red (TRPV4 antagonist) or TRPV4 antisense oligonucleotide (TRPV4 AS)	Intrathecal	Rat lumbar DRG compression injury	Ding et al. (2010)	Some reversal of thermal hyperalgesia, decreased nitrite in DRG
Soluble guanylate cyclase inhibitor (1H-[1,2,4]-oxadiazolo[4,3-a] quinoxalin-1-one, ODQ)	Intrathecal or perineural	Rat lumbar DRG compression injury, rat lumbar nerve root compression via steel rod	Song et al. (2006), Ding et al. (2010)	Some reversal of thermal hyperalgesia
8-(4-chlorophenylthio)-guanosine 3′,5′-cyclic monophosphorothioate	Intrathecal	Rat lumbar DRG compression injury	Ding et al. (2010)	Some reversal of thermal hyperalgesia

(continued)

Table 19.2 (continued)

Agent	Route	Model description	Reference	Observations
PKA antagonist (SQ22536)	Perineural	Rat lumbar nerve root compression via steel rod	Song et al. (2006)	Some reversal of thermal hyperalgesia
NF-kappa B decoy-FITC	Intrathecal	Rat L5 DRG compression and NP placement	Suzuki et al. (2009)	Reversed molecular changes in DRG, partly reversed mechanical allodynia, and thermal hyperalgesia
PKG inhibitor Rp-isomer sodium salt (Rp-8-pCPT-cGMPS)	Intrathecal	Rat lumbar nerve root compression via steel rod, rat lumbar DRG compression injury	Song et al. (2006), Ding et al. (2010)	Some reversal of thermal hyperalgesia
Protease or cytokine inhibitors				
Hydroxamic acid-based metalloproteinase inhibitor, TAPI	Epineural	Rat sciatic nerve constriction injury	Sommer et al. (1997)	Reduced thermal hyperalgesia and mechanical allodynia, reduced TNF immunoreactivity in epineurium
sTNFRI	Intrathecal or systemic	Lumbar or cervical nerve root compression with, or without chromic gut exposure	Winkelstein et al. (2001a), Rothman et al. (2009b, 2010)	Some reversal of mechanical allodynia, reduced spinal astrocytic reactivity
sTNFRII	Systemic i.p. or local (perineural)	Rat constriction nerve injury or ligation, rat DRG exposure to NP	Schafers et al. (2003), Allen et al. (2011), Zanella et al. (2008)	Some reversal of allodynia, restored normal gait
IL-1Ra	Intrathecal or systemic	Lumbar or cervical nerve root compression with or without chromic gut exposure	Winkelstein et al. (2001b), Rothman et al. (2009b, 2010)	Some reversal of allodynia, and reduced spinal astrocytic reactivity
Salmon fibrin and thrombin	Perineural	Rat cervical nerve root compression	Weisshaar et al. (2011)	Partly reversed mechanical allodynia and reduced macrophage recruitment

radiculopathy, and they appear to have some efficacy as measured with both objective (e.g., straight-leg raising test) and self-reported outcomes (e.g., VAS) (Buenaventura et al. 2009; Staal et al. 2008). Methylprednisolone and other corticosteroids may work by inhibiting the increase in endoneurial vascular permeability and the decrease in nerve conduction velocity that follows injury to the nerve root upon exposure to nucleus pulposus tissue or chemical injury (Byrod et al. 2000; Olmarker et al. 1994). Regardless of the mechanism, use of these NSAIDs and corticosteroids is generally considered safe and a first line of treatment for patients presenting with pain from intervertebral disc herniation.

The current standard of care does not address the underlying pathology of intervertebral disc herniation, which clearly involves inflammatory, proteolytic, and immune-mediated pathways. As new knowledge from animal models is gained, an understanding of the role of inflammatory mediators in mediating responses to nerve root injury has emerged; the focus here is on cytokines that regulate immune system involvement, such as TNF-α, or those that mediate pain sensitivity such as α2 adrenergic receptor and serotonin receptor antagonists. Pharmacological approaches that target perception of pain and restoration of functional losses with radiculopathy, as well as those that influence disease pathways, have great potential to reduce the duration of symptoms and disability associated with disc herniation and may even play a role in reducing the need for surgical intervention. Here, we will briefly review ongoing investigations to pharmacologically treat radiculopathy associated with disc herniation and to identify those with the most promising therapeutic potential.

19.4.1 Cytokine Antagonism

Given the documented increase of TNF-α and IL-1β expression in degenerated and herniated discal tissues, as well as clear evidence of a role for the cytokine TNF-α in reproducing many symptoms of radiculopathy in animal models (Allen et al. 2011; Olmarker 2001; Onda et al. 2002; Rothman and Winkelstein 2010; Winkelstein et al. 2001a), cytokine antagonism has received considerable attention. In our prior studies, we have demonstrated an ability for IL-1β antagonists (IL-1Ra or Kineret™) to partially reverse mechanical allodynia and spinal astrocytic reactivity following nerve root compression (Rothman and Winkelstein 2010; Winkelstein et al. 2001a, Table 2). The finding that TNF antagonists (blocking antibodies) influence peripheral nerve injury (DeLeo et al. 2000; Lindenlaub et al. 2000; Sommer et al. 2001) and attenuate allodynia in constriction injury models, and that overexpression of TNF could elevate allodynia in the same model, has evoked considerable interest in this class of compounds. Application of exogenous TNF-α to lumbar nerve roots in the rat reproduces many of the neurophysiology changes described earlier for compression-induced nerve root injury, including decreased nerve conduction velocity, glial activation, and inflammatory changes in the ganglion (Aoki et al. 2002; Igarashi et al. 2000;

Onda et al. 2002; Ozaktay et al. 2002). Furthermore, systemic treatment with the TNF-blocking antibody, Remicade® (infliximab, intravenous or intraperitoneal), reduced pain-related movements in rats, as well as the expression of key neurotrophins in the DRG and spinal cord (Murata et al. 2004b; Olmarker et al. 2003; Olmarker and Rydevik 2001; Onda et al. 2004; Sasaki et al. 2007). In other animal studies, including our own, local delivery of a soluble TNF receptor type II analogue (etanercept or Enbrel®) has been shown to restore normal gait patterns and reverse the heightened allodynia response to nucleus pulposus placement upon the DRG as a model of intervertebral disc herniation (Allen et al. 2011; Cuellar et al. 2004). These results add strength to the notion that TNF inhibition can attenuate or reverse changes in animal locomotion, nerve electrophysiology, and pathology due to nucleus pulposus exposure in the short term (<7 days). For these reasons, the hypothesis has evolved that, in response to disc herniation, TNF-α serves as the critical cytokine mediating nerve sensitivity and inflammation. This plausible mechanism is supported by the elevated tissue levels of TNF-α in the degenerative disc as well the increased number of activated macrophages and lymphocytes in herniated tissue fragments that secrete the cytokine. Thus, it is plausible that TNF-α contributes, at least in part, to the perception of pain and promotes neuroinflammation following disc herniation. For this reason, to date, clinical studies that target symptoms of disc herniation-associated radiculopathy have focused largely on TNF antagonists.

In a first study of TNF inhibitors to antagonize pain associated with intervertebral disc herniation, patients with a history of herniation-associated sciatica (average duration of symptoms = 7 weeks) were given a single intravenous infusion of infliximab ($n = 10$, 3 mg/kg, Karppinen et al. 2003) or treated with periradicular saline as a "historical control" ($n = 62$). Outcomes of visual analogue scale (VAS), straight-leg raising test, low back pain severity, and Oswestry Disability Index were measured at baseline and out to 3 months after treatment. All outcomes outperformed the saline control, with the exception of a decrease in leg pain reported at 1 h after the infusion, and sustained out to 3 months (88 and 51 % change from baseline, infliximab vs. saline). Similar changes supportive of infliximab treatment were noted in low back pain severity, straight-leg raising test results, the Schöber index, and the Oswestry index. No patients required surgery and none experienced adverse effects of infliximab, while motor and sensory loss resolved in patients within 1–3 months. A later study evaluated the efficacy of subcutaneous injections of etanercept (25 mg every 3 days, 3 injections) in ten patients with acute severe sciatica (mean symptom duration of 2–7 weeks (Genevay et al. 2004)). Visual analogue scales (VAS) for leg and back pain, as well as Oswestry Disability Index and modified Roland–Morris Disability Questionnaire, were obtained after 10 days and 6 weeks. A good clinical response was observed in nine or ten patients at 6 weeks after treatment, although no control group was cited in this study. Over the years, multiple clinicians have individually described case reports of their experiences with delivery of infliximab or etanercept for the treatment of disc herniation-related radiculopathy that was otherwise nonresponsive to treatment (Atcheson and Dymeck 2004; Tobinick and Britschgi-Davoodifar 2003). Decreases in pain scores and improved disability indices are generally reported, leading to the emergence of TNF inhibitors as available strategies for clinical treatment of pain associated with intervertebral disc herniation.

The first randomized controlled trial of TNF antagonism for radiculopathy (termed FIRST II, Finnish Infliximab Related Study) (Korhonen et al. 2006; Korhonen et al. 2005) was reported in 2006. Patients ($n = 40$ with symptomatic disc herniation on MRI, leg pain <12 weeks. ≤60° on the straight-leg raising test) were treated with a single intravenous infusion of infliximab (5 mg/kg) and compared against a placebo. Straight-leg raise, motor and sensory defects, leg and back pain (VAS), Oswestry disability, quality of life (RAND-36), and more parameters were compared between the treatment and placebo groups out to 1 year following treatment. Results were not supportive of infliximab therapy, however, with 67 and 63 % of all patients reporting no pain in the infliximab and placebo groups, respectively. Similar values were observed between treatment groups for other outcomes, although a subgroup of patients in the infliximab group appeared to especially benefit from the infliximab treatment (an L4–L5 or L3–L4 herniation with a Modic change at the symptomatic level). The authors concluded that further study of this subgroup of patients may yield insights about the potential for TNF antagonists to modify clinical outcomes for intervertebral disc herniation.

A recent study of epidural etanercept for radiculopathy (Cohen et al. 2009) provided a more promising result. Patients with unresolved symptoms ($n = 12$, >2 months in duration) received 2 injections of etanercept (2, 4, or 6 mg). A majority of patients noted complete resolution of pain by 3 months after treatment with etanercept; this was much higher than the 17 % for the epidural saline control group. While a small study, it nonetheless illustrates the potential for local administration of TNF antagonists to modify radicular pain associated with disc herniation.

19.4.2 Neuronal Receptor Blockers

Another set of targets proposed for the treatment of intervertebral disc herniation-associated pain centers around blocking receptors involved in neuronal activation. Compounds shown in Table 19.2 generally act by competitively binding to receptors that control neuronal excitation and downstream effectors. When delivered systemically, their activity is not localized to the affected nerve and can involve the CNS

and other sites. In preclinical models, an NMDA receptor antagonist, administered systemically following sciatic nerve ligation, reversed mRNA changes induced by peripheral nerve constriction (Uceyler et al. 2008). When administered locally, this NMDA receptor antagonist was also capable of partly reversing motor deficits and allodynia following lumbar spinal nerve ligation (Chaplan et al. 1997). In animal models, the GABA analogue, gabapentin, whether delivered locally or systemically also caused a similar reversal of allodynia (Abe et al. 2002; Zanella et al. 2008). Indeed, orally prescribed gabapentin has been shown to relieve symptoms associated with radiculopathy from lumbar disc herniation when measured by the VAS or self-reported disability indices; on the other hand, systemic delivery is associated with frequent and adverse side effects (Kasimcan and Kaptan 2010; Yildirim et al. 2009). Nevertheless, this class of receptor blockers appears to be of use for the treatment of radiculopathy and superior to nonsteroidal anti-inflammatory drugs, especially when delivered locally.

The serotonin receptor, 5-HT(2A), blocker, sarpogrelate hydrochloride, has been used for both animal model and clinical studies for the treatment of sciatica. In a rat model, 5-HT(2A) receptor blockers were shown to decrease blood flow to a nerve inflamed by placement of nucleus pulposus tissue upon the nerve root and to reverse allodynia (Hashizume et al. 2007; Sekiguchi et al. 2008). In patients, high doses (300 mg) of sarpogrelate hydrochloride given orally led to significant improvements in VAS scales of sciatic pain in a majority of patients, with few patients (<20 %) needing to go on to surgery (Kanayama et al. 2003). Patients with an "uncontained disc herniation," or one that is extruded or sequestered from the parent disc, responded more favorably to the 5-HT(2A) blocker treatment with few side effects, suggesting this approach may be useful for alleviating symptoms associated with intervertebral disc herniation.

19.4.3 Cell Cycle Modifiers

A number of therapeutic approaches have been proposed to target the microglia that are believed to be activated early in the inflammation cascade that follows compression or chemical injury to the nerve root. The neuroprotective antibiotic minocycline, as well as the antimetabolite methotrexate, attenuates allodynia induced by DRG constriction injury, yet does not appear to act through attenuation of glial activation following injury (Table 19.2).

19.4.4 Pathway Inhibitors

New developing therapies that target the NF-κB or protein kinase pathways have been proposed (Table 19.2). Results of animal studies show that pathway inhibitors are able to partly reverse thermal hyperalgesia induced by DRG compression or nucleus pulposus placement. Importantly, inhibition of NF-κB, a key mediator of TNF-α signaling, appears to also reverse changes in the mRNA profile downstream of DRG compression. As for cell cycle modifiers, additional studies are required to promote the concept that any specific inhibitor can influence neuroinflammation linked to intervertebral disc herniation.

19.5 Final Comments

This review focuses on pathological events associated with disc herniation, in particular the grade of nerve root compression and the exposure and presence of nucleus pulposus tissue. The impact of herniation can thus be viewed as not one disorder, but perhaps two or three distinct conditions that can benefit from distinctly different therapeutic approaches. A contained or protruding herniation that is linked to prolonged nerve root compression may be associated with electrophysiological changes that can benefit from early intervention including the use of agents to attenuate glial activation and mediate pain sensitivity (e.g., neuronal receptor modifiers). An uncontained or extruded disc herniation that has components of both nerve root compression and tissue-mediated inflammation may be better addressed with a combined anti-inflammatory approach including the use of cytokine antagonists and protein kinase or NF-κB inhibitors. In all cases, it appears that systemic delivery of these agents will be associated with lower efficacy and higher risk of side effects than local drug delivery; this view is supported by the increased interest in epidural administration of immunosuppressants like the TNF antagonists and advancement of novel, depot-based delivery systems (Hubbard et al. 2009; Shamji et al. 2008; Zanella et al. 2008). Of course, surgery for disc fragment removal remains an option for patients that are nonresponsive to pharmacologic and alternate approaches. However, it is becoming clear that residual and persistent hypersensitivity from long-term nerve root compression can be a deleterious event and a constant source of intense pain. Thus, demand will continue for strategies that attenuate the neuropathy associated with intervertebral disc herniation, shorten the symptom period, and promote functional recovery.

19.6 Summary of Critical Concepts Discussed in the Chapter

Fragments of intervertebral disc that "herniate" into the extra-discal space and impinge upon, or contact, the spinal nerve roots can cause significant pain, neurological deficits,

and functional disability in a large number of affected individuals.

- Nerve root impingement due to a herniated disc can result in nerve root pathophysiology, including edema, inflammation, disorganization of the myelin sheath, decreased axonal packing, Wallerian degeneration of the peripheral axons, and loss of axonal transport and decreased amplitudes of evoked action potentials.
- Nerve root changes are associated with developing hypersensitivity to non-noxious (allodynia) and noxious stimuli (hyperalgesia) that serve as useful indicators of neuropathic pain in both human subjects and animals.
- The magnitude, duration, and rate of compression of the nerve root promote local nerve root damage and the degree and duration of the pain symptoms.
- Herniated intervertebral disc exhibits increased angiogenesis, macrophage and lymphocyte infiltration, and proinflammatory cytokine and proteinase activity that can contribute to sustained painful symptoms over a period of months to years.
- Herniated disc fragments may activate the immune system when in contact with the systemic circulation, glial cells of the affected nerves, and the central nervous system (microglia and astrocytes). The activated microglia will release increased levels of neurotransmitters from presynaptic neurons, sensitize the postsynaptic membrane, activate neighboring astrocytes, and enhance microglial activity. Hence, the initiation of nerve root damage by a herniated disc can drive a positive feedback loop that can promote a sustained painful neuropathy.
- While surgical removal of the herniated disc fragment can alleviate many of the pathological symptoms, pharmacological interventions and lifestyle modifications are the first line of treatment for pain from disc herniation.
- The use of NSAIDs and corticosteroids with herniation-associated radiculopathy is safe, but provides no means to modify pathology or outcomes. Emerging pharmacological therapies provide some promise here and are focused on antagonizing the many proinflammatory cytokines implicated in radiculopathy, most notably tumor necrosis factor (TNF-α).
- Pharmacologic interventions that show promise in the treatment of herniation-associated radiculopathy include the class of competitive inhibitors of neuronal receptors (e.g., serotonin receptor antagonists), inhibitors of glial proliferation (e.g., minocycline) or metabolism (e.g., methotrexate), and inhibitors of the cellular inflammatory pathways (e.g., NF-κB or PKC inhibitors).
- Additional work is needed to reveal the role of central nervous system sensitization and remodeling in response to disc herniation and to better understand its role in the persistent neuropathy.

In summary, there is a growing demand for strategies that attenuate neuropathy associated with intervertebral disc herniation and shorten the duration of pain and functional recovery.

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