

Neuropathology Of Discogenic Low Back Pain: A Review

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Abstract

Under normal physiological conditions, lumbar intervertebral discs are less sensitive to nociceptive stimuli than other spinal tissues. Therefore, it is likely that some pathological changes may be present in painful lumbar discs. Previous reports describe nerve fibers extending into the painful disc rather than being restricted to the outermost area as found in asymptomatic discs. This difference may play an important role in the generation of discogenic pain, which is the pain produced by intervertebral disc disorders. It has been reported that inflammatory mediators, nerve growth factor (NGF), and a decrease of proteoglycan content have the potential to promote nerve ingrowth into the disc. Furthermore, recent reports suggested that the levels of inflammatory mediators and NGF are higher in painful discs than in asymptomatic discs. Nerve ingrowth into painful discs may therefore be regulated by multiple factors, including factors as yet unidentified. Also, the inflammatory mediators and NGF have a sensitizing effect on nerve fibers. In summary, we suppose that nerve ingrowth into the disc and sensitization of the disc afferents would be two major neuropathogenic mechanisms for chronic discogenic pain.

INTRODUCTION

Disorders of the lumbar intervertebral disc generate discogenic pain, which is considered to be a major source of low back pain.¹ Clinically, disc herniation is preceded by one or more attacks of acute low back pain.¹ Recently, Hyodo et al. demonstrated that intradiscal injections of local anesthetics and steroids eliminated acute low back pain in patients with a radial annular tear,² which suggests an annular tear is a cause of acute low back pain. Generally, pain sensation is generated when nociceptive nerve endings are subject to noxious stimuli. Therefore, if an annular tear reaches nociceptive nerve endings, it may cause acute discogenic low back pain.

Clinically, acute discogenic low back pain frequently disappears within one to two weeks. This seems reasonable because an annular tear may heal after adequate follow-up. However, in some cases, acute discogenic low back pain can become chronic. Chronic discogenic low back pain is quite difficult to treat and has a major socio-economic impact. Despite its clinical importance, the pathogenesis of chronic discogenic pain is poorly understood.

Disc degeneration is thought to be one of the causes of chronic discogenic low back pain. However, disc degeneration is commonly observed in patients without low back pain, suggesting that the correlation between disc

degeneration and pain is not clear cut.^{3, 4} Accordingly, we should pay attention to the differences between the degenerated disc and the painful disc. Because a tissue cannot generate pain without nerve structures, it is important to know the neuropathology of a painful disc to shed light on the mechanism of discogenic pain.

To achieve this purpose, the innervation of the normal lumbar intervertebral disc must first be understood. Then, it is necessary to determine whether the innervation of the painful disc is different from that of the normal disc. Previous studies demonstrating such differences between painful and asymptomatic discs may help us understand the neuropathology of discogenic pain.^{5,6,7}

INNERVATION OF THE LUMBAR INTERVERTEBRAL DISC

The presence of sensory fibers in the lumbar intervertebral disc of humans,^{8,9,10,11,12,13} rats,^{14,15,16} and other animal^{17, 18} has been described. Also, it has also been reported that substance P (SP) and calcitonin gene-related peptide (CGRP)-immunoreactive (-IR) nerve fibers are present in the disc.^{9, 11, 16, 19,20,21} Because SP and CGRP are both expressed in nociceptive neurons and their axons,^{22, 23} these SP- and CGRP-IR disc nerve fibers are thought to be involved in transmitting nociceptive information from the disc. Therefore, the presence of SP- and CGRP-IR nerve

fibers suggests that the disc itself could be a source of pain.

On the other hand, there are two important findings which are closely related to the generation of discogenic low back pain.^{11,24} First, it is generally recognized that the innervation of the disc is very sparse,¹¹ and restricted to the outermost part of the annulus fibrosus,^{5, 7, 10, 12, 13} and endplate.^{25, 26} Bogduk et al. reported that nerve fibers were present only within the outer one third of the annulus fibrosus.¹⁶ More recently, it was described that the normal disc is only innervated to a depth of up to 3.5 mm.¹² Autonomic fibers seem to extend deeper into the annulus fibrosus than nociceptive fibers.¹² This indicates that an annular tear confined to the inner annulus would not cause low back pain. Second, Yamashita et al. used electrophysiological techniques to demonstrate that intervertebral discs are less sensitive to noxious stimulation than other spinal structures, such as paravertebral muscles and facet joints.²⁴ These two findings suggest that the lumbar intervertebral disc would rarely cause low back pain, except in the case of an annular tear reaching the outermost part of the annulus fibrosus. Also, if an annular tear does occur and causes acute discogenic low back pain, the symptoms usually disappear within a short period, as previously stated. Currently, there is no explanation for the persistence of chronic pain after an annular tear completely heals. However, low back symptoms may instead continue and even become chronic in some cases. Thus, we believe that some pathological changes occur in the disc during the development of chronic discogenic pain.

NERVE INGROWTH IN THE “PAINFUL INTERVERTEBRAL DISC”

In 1970, Shinohara, using a silver impregnation technique, described the presence of nerve fibers in the inner annulus and nucleus pulposus obtained from patients with discogenic disorders.²⁷ He hypothesized that scar tissues are formed in degenerated discs and nerve fibers accompany the scar tissues into the disc. Using immunohistochemistry, Coppes et al. described the presence of SP-IR nerve fibers in the inner layers of the annulus fibrosus and nucleus pulposus.^{5, 6} Because SP is implicated in pain sensation, the presence of SP-IR nerve fibers indicates that the disc can be the source of pain. Importantly, innervation of the inner disc was observed only in painful discs, not in control discs. However, in these studies, there appears to be an inadequate number of control discs.

Following these studies, Freemont et al. examined the

innervation of the inner disc using 46 biopsy samples (30 from levels with pain and 16 from levels with no pain).⁷ In this study, innervation of the inner disc was observed more frequently in painful discs than in asymptomatic discs. They further demonstrated the presence of growth-associated protein-43 (GAP-43)-IR fibers in inner painful discs. Because GAP-43 is recognized to be a marker of axonal growth, these findings strongly suggest that nociceptive nerve fibers were growing into the painful disc. From these observations, nerve ingrowth into the inner disc appears to be a possible cause of chronic discogenic low back pain.

POSSIBLE FACTORS REGULATING NERVE INGROWTH

In the normal disc, nerve fibers rarely extend into the inner layers of the disc. Several factors may prevent nerve ingrowth into the disc in physiological states. Previous reports proposed that proteoglycans might be one of those factors,^{28, 29} because proteoglycans are thought to be implicated in the regulation of neurite growth in the central nervous system.³⁰ Molecular details of the inhibitory effects of proteoglycans on axonal growth are still unknown. However, they could bind to a neuronal surface receptor or to a membrane component near the receptor, resulting in the inhibition of axonal growth.³⁰

Using sheep annular lesion models, Melrose et al. showed that nerve ingrowth into the disc was inversely correlated to proteoglycan levels, suggesting the inhibitory effect of proteoglycans on nerve ingrowth.²⁸ In addition, they described nerve fiber extending into the inner disc three months after the annular lesion.²⁸ Johnson et al. demonstrated that disc aggrecan inhibits nerve fiber growth in vitro.²⁹ These reports indicate that a decrease in proteoglycan levels, which is normally associated with disc degeneration,^{28, 31} provides nerve fibers an opportunity to extend more deeply into the disc. More recently, Akeda et al. found that Neural-Glial antigen 2 (NG2) proteoglycan, which has inhibitory effects on axonal growth in vitro,³² is extensively distributed in the disc.³³ All of these factors may inhibit nerve ingrowth into the normal disc. Also, we suppose that the tight collagen network of the normal annulus fibrosus could serve as a physical barrier to nerve ingrowth.

Although a substantial proportion of degenerated discs are asymptomatic,^{3, 4} these findings lead us to conclude that disc degeneration is one of the factors promoting nerve ingrowth into the disc. Salminen et al. found that disc degeneration in

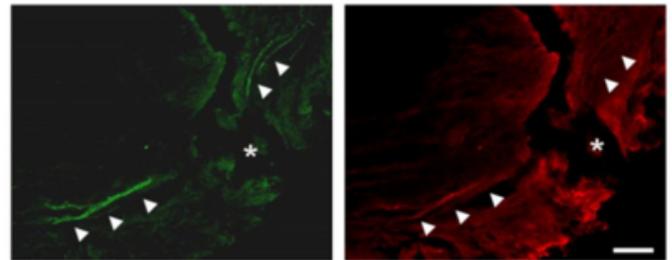
adolescents is predictive of recurrent or persistent low back pain,³⁴ suggesting the importance of genetic factor in the development of discogenic pain. Disc degeneration is reported to be associated with several genes encoding collagen type IX,³⁵ aggrecan,³⁶ the vitamin D receptor,^{37, 38} and a cartilage intermediate layer protein.³⁹ However, there is no study describing a correlation between a specific gene and discogenic pain. Further study is needed to determine if a specific gene plays a role in generating discogenic pain.

Recently, Burke et al. examined the production of inflammatory mediators in lumbar intervertebral discs.⁴⁰ They found the levels of inflammatory mediators were higher in painful discs than in asymptomatic discs. These results indicate that disc inflammation may persist in those patients with discogenic pain.

More recently, we demonstrated the possibility that disc inflammation promotes the axonal growth of dorsal root ganglion (DRG) neurons into the disc.⁴¹ To determine the DRG neurons which innervate the lumbar disc, a neurotracer, Fluoro-Gold (FG; Fluorochrome, Denver, CO) was applied to lumbar discs of rats. We found that the percentage of FG-labeled neurons expressing GAP-43 was increased three days after the application of complete Freund's adjuvant (CFA) into the disc. This result indicates that CFA-induced inflammation of the disc may induce axonal growth of DRG neurons innervating the disc. Our immunostaining study also revealed that GAP-43-IR nerve fibers were more frequently observed in the inflamed discs than in the non-inflamed discs (Figure 1), which suggests that disc inflammation could potentiate nerve ingrowth into the disc.

Figure 1

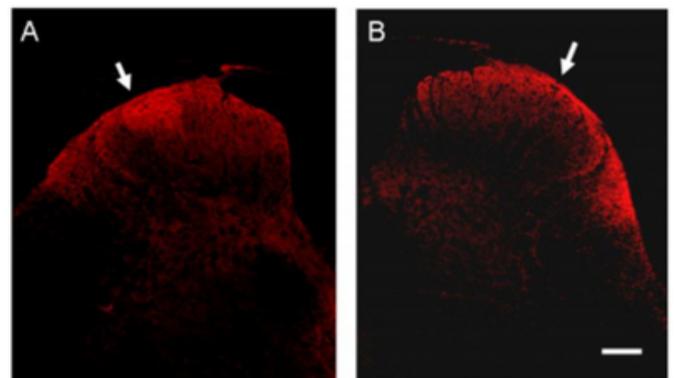
Figure 1: Fluorescent photomicrographs showing calcitonin gene-related peptide (CGRP)-positive nerve fibers (A) and growth-associated protein (GAP-43)-positive nerve fibers (B) in the rat L5-L6 intervertebral disc. Panel B is the same section as panel A. The asterisk indicates the complete Freund's adjuvant (CFA) application site. Arrowheads indicate CGRP-positive (A) and GAP-43-positive (B) nerve fibers running parallel to the outer layer of the annulus fibrosus in the vicinity of the CFA application site. Scale bar 100 μm .



We observed that the area of GAP-43-IR staining in the corresponding level of the dorsal horn was markedly expanded on the side to which CFA was applied. (Figure 2).

Figure 2

Figure 2: Fluorescent photomicrographs of the dorsal horn of the rat spinal cord stained by immunohistochemistry for growth-associated protein-43 (GAP-43). Panels A and B are from the same level of the spinal cord (L2 segment). The GAP-43-IR area is more densely and broadly observed on the side of complete Freund's adjuvant application (A) than on the contralateral side (B). Scale bar 200 μm .



Although we could not exclude the possibility that inflammation of the iliopsoas muscle affected the data, disc inflammation might have induced axonal sprouting in the dorsal horn. Because reorganization of the sensory network in the dorsal horn could cause chronic pain,⁴² disc inflammation would appear to be important in the generation of chronic discogenic pain.

Freemont et al. demonstrated that nerve growth factor (NGF)

is present in the painful discs, but not in asymptomatic discs.⁴³ They also showed the presence of high-affinity NGF receptor, trk-A-expressing nerve fibers in the painful discs. In addition, our recent study suggested that almost all of the nociceptive DRG neurons innervating the rat disc belong to a subgroup of neurons which is sensitive to NGF.^{44, 45} Considering its neurotrophic activity, NGF may also be a factor promoting nerve ingrowth into painful discs.

In summary, nerve ingrowth into the disc may be regulated by a balance between promoting factors and inhibitory factors. If a lesion occurs in the disc and changes that balance, nerve fibers could grow into the disc and might generate discogenic low back pain.

SENSITIZATION OF THE NEURONS INNERVATING THE LUMBAR INTERVERTEBRAL DISC

As previously stated, lumbar intervertebral discs are normally less sensitive to nociceptive stimuli.²⁴ Clinically, discography is used as a diagnostic tool for patients with discogenic pain. The criterion for a positive discogram is a concordant pain response during the disc injection.⁴⁶ Painful discs produce intense pain with even a low pressure injection, whereas asymptomatic discs resist pain with a high pressure injection.

As reviewed by Cohen et al., the concept of chemical sensitization may explain the different responses between painful and asymptomatic discs.⁴⁷ Tumor necrosis factor- α (TNF- α) is expressed in the nucleus pulposus^{48, 49} and plays a role in generating sciatic pain in patients with disc herniation.⁵⁰ Interleukin-1 β (IL-1 β), which is thought to be produced in tissues at disc herniation, has the capacity to produce hyperalgesia.⁵¹ Also, NGF, which is upregulated by such mediators, has a sensitizing effect on nerve fibers.^{51, 52} It has previously been reported that the levels of inflammatory mediators and NGF are higher in painful discs than in asymptomatic discs,^{40, 43} suggesting that they may play a role in sensitizing the painful disc.

Recently, we reported that most of the DRG neurons innervating the disc are NGF-sensitive neurons, which are closely related to the inflammatory pain state.^{44, 45} In inflammatory states, NGF, which is synthesized in inflamed tissue, acts to upregulate the expression of various pain-related molecules in primary afferent neurons and sensitizes them,^{53, 54} consequently producing hyperalgesia.^{51, 55, 56, 57, 58} Thus, we suppose that NGF synthesized in inflamed discs may increase nociceptive sensitivity of DRG neurons

innervating the lumbar disc. From these observations, disc inflammation is critical for sensitizing the neurons innervating the disc. However, sensitization would not occur without the exposure of annular nerve endings to the chemical irritants. If the nerve fibers extend into the disc, it is more likely that the inflammatory mediators reach the nerve ending to sensitize them.

We conjecture that “sensitization of the disc” may explain why even a low-pressure injection may induce a concordant pain, whereas a high-pressure injection may not induce pain in asymptomatic discs. Currently, the validity of discography is still arguable, because of the relatively high incidence of false-positive results.^{59, 60} However, from the neuropathological point of view, discography seems to be a reasonable diagnostic tool for sensitized discs.

The intervertebral disc is under constant mechanical stress and increased intervertebral motion is related to the generation of discogenic pain.⁶¹ If “sensitization of the disc” occurs, the increased mechanical stress is likely to play a role in activating the sensitized nerve endings. However, if the disc is not sensitized, it is possible that the increased mechanical stress does not cause discogenic pain.

CLINICAL IMPLICATION

Disc herniation causes disruption of the tight collagen network of the annulus. Following disc herniation, the ruptured disc would heal with the formation of scar tissue, which may induce the production of inflammatory mediators.^{62, 63} In addition, the scar tissue would provide nerve fibers with a path to grow into the disc.

Clinically, not all patients with disc herniation develop chronic discogenic low back pain. However, if disc degeneration is already present in the ruptured disc, the lower level of proteoglycan content may facilitate nerve ingrowth into the disc. We believe that nerve ingrowth into the disc is at least one of the possible causes of discogenic pain. Because other unknown factors affecting nerve ingrowth into the disc may exist, further investigations are needed to identify those factors and their relationship to this nerve ingrowth.

In summary, we think that nerve ingrowth into the disc and sensitization of the disc afferents would be two major neuropathogenic mechanisms for chronic discogenic pain.⁶⁴ If so, treatments for chronic discogenic pain should be targeted to these neuropathological changes. Although lumbar interbody fusion may completely alleviate the

symptoms, other interventional therapies may have some limitations.

Corticosteroids are widely used for the treatment of patients with chronic discogenic pain, although their efficacy remains controversial.^{65,66,67} Recently, it was reported that application of TNF- α inhibitors and IL-1-receptor antagonist protein into the disc was effective for the treatment of discogenic pain.^{68,69} Previous studies suggest that neutralizing NGF using anti-NGF or a TrkA-IgG fusion molecule may prevent hyperalgesia induced by inflammation and nerve injury.^{70,71,72,73,74} Our studies revealed that the lumbar intervertebral disc is more sensitive to NGF than other tissues, suggesting that neutralizing NGF might be more effective for discogenic low back pain than other pain states.^{45, 64, 75} These anti-inflammatory drugs may reduce sensitization of the disc afferents. However, the drugs may not improve the extensive innervation.

Recently, the minimally invasive intradiscal electrothermal therapy (IDET) has reportedly been used to treat discogenic pain.⁷⁶ IDET might destroy nociceptive fibers extending into painful discs. However, IDET might accelerate degeneration of the disc and cause inflammation. Clinically, the efficacy of IDET remains controversial at this time.^{77,78,79,80,81,82}

Disc repair is expected to be a future treatment for discogenic pain.^{83,84,85} This approach increases proteoglycan synthesis and normalizes the intradiscal environment; however, further study is needed to discover whether it relieves discogenic pain.

In order to develop effective treatments for discogenic pain, it is essential to first understand the neuropathology of discogenic pain.

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