Sensory nerve ingrowth, cytokines, and instability of discogenic low back pain: A review

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Abstract:

Introduction: Many patients suffer from discogenic low back pain. However, the mechanisms, diagnosis strategy, and treatment of discogenic low back pain all remain controversial. The purpose of this paper was to review the pathological mechanisms of discogenic low back pain.

Methods: Many authors have investigated the pathological mechanisms of discogenic low back pain using animal models and examining human patients. Central to most investigations is understanding the innervation and instabilities of diseased intervertebral discs and the role of inflammatory mediators. We discuss three pathological mechanisms of discogenic low back pain: innervation, inflammation, and mechanical hypermobility of the intervertebral disc.

Results: Sensory nerve fibers include C-fibers and A delta-fibers, which relay pain signals from the innervated outer layers of the intervertebral disc under normal conditions. However, ingrowth of these sensory nerve fibers into the inner layers of intervertebral disc occurs under disease conditions. Levels of neurotrophic factors and some cytokines are significantly higher in diseased discs than in normal discs. Stabilization of the segmental hypermobility, which can be induced by intervertebral disc degeneration, suppresses inflammation and prevents sensitization of sensory nerve fibers innervating the disc.

Conclusions: Pathological mechanisms of discogenic low back pain include sensory nerve ingrowth into inner layers of the intervertebral disc, upregulation of neurotrophic factors and cytokines, and instability. Inhibition of these mechanisms is important in the treatment of discogenic low back pain.

Keywords: low back pain, mechanisms, intervertebral disc

Introduction

Low back pain affects much of the world’s population, and has significant adverse socioeconomic implications. The one-time occurrence of low back pain is about 15%-30% of the population; the one-month prevalence is 19%-43% of the population; and the lifetime prevalence is up to 60%-80% of the population1). Age distribution of discogenic low back pain was thought to be 36-47 years old, which is significantly younger than that in patients suffering low back pain from a facet joint or sacroiliac joint origin2). Age distribution of discogenic low back pain was thought to be 36-47 years old, which is significantly younger than that in patients suffering low back pain from a facet joint or sacroiliac joint origin2). We have previously reported that animal models and specimens from humans have revealed sensory innervation of lumbar intervertebral discs and sensory nerve ingrowth into the inner layer of intervertebral discs, causing painful conditions3). Cytokines such as tumor necrosis factor-α and interleukins induce this ingrowth. Nerve growth factor has also been recently identified as an inducer of ingrowth4). Finally, disc degeneration induces several collagens; their action results in hypermobility and pain5).

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Mechanical Disc Degeneration trunks and reach the L2 DRGs fibers are thought to enter the paravertebral sympathetic at upper levels. In nonsegmental innervation, sensory nerve the corresponding level and in multiple segments by DRGs other animal study, sensory nerve fibers from the lower in-

Figure 1. Pathomechanisms of discogenic low back pain. Innervation: animal model and specimens from humans revealed sensory nerve innervation of lumbar intervertebral discs (IVDs) and sensory nerve ingrowth into the inner layer (deep nerve in-
growth) of the degenerated IVD. Inflammation: many researchers have identified various proinflammatory molecules. Hypermobility: hypermobility of motion segment is usually induced in de-
generated IVD. These factors are thought to be the major factors that induce discogenic low back pain.

In this paper, we review innervation, inflammation, and mechanical hypermobility of discogenic low back pain from studies of animal and humans (Fig. 1).

Innervation

The vertebra, disc, facet joint, posterior longitudinal liga-
ment (PLL), and dura mater are innervated segmentally by the dorsal ramus and the sinu-vertebral nerves branching from the spinal nerve of the corresponding levels (8-12). Many studies have described the existence of sensory nerve end-
ings in the annulus fibrosus (11,16). It is believed that such nerve endings originate from the sinu-vertebral nerves branching from the ventral ramus of the spinal nerve and the ramus communicans of the corresponding level (10). However, the level of the spinal cord or dorsal root ganglia (DRG) innervating the intervertebral disc has not been elucidated.

Takahashi et al. have reported direct evidence for groin pain corresponding to the L2 dermatome referred from the L4/5 intervertebral disc using an animal model (79). Using another animal study, sensory nerve fibers from the lower inter-
vertebral disc are thought to be innervated by DRGs at the corresponding level and in multiple segments by DRGs at upper levels. In nonsegmental innervation, sensory nerve fibers are thought to enter the paravertebral sympathetic trunks and reach the L2 DRGs (6-10).

Human sensory innervation to intervertebral disc.

Patients who have degenerated lumbar discs in lower seg-
ments (L4-L5 or L5-S1) occasionally report groin pain (20-23). Yukawa et al. reported that 21 of a total of 512 patients (4.1%) with groin pain were diagnosed with singular lower lumbar disc herniation (L4-L5 and L5-S1), and concluded that the sinu-vertebral nerve that innervates the posterior an-

Inflammation

Human samples

Multiple authors have reported pain-related molecules, in-
cluding tumor necrosis factor (TNF) alpha, Interleukin (IL)-
1 beta, IL-4, IL-6, IL-8, IL-12, prostaglandin E2 (PGE2),

Pathogenesis of sensory nerve ingrowth into intervertebral discs causing painful conditions.

Some investigators disagree with the notion that nerve endings in the intervertebral disc are present in the intervertebral disc and thereby deny the possibility of pain originating from discs them-

 selves (22-26). There is evidence to support the idea that sensory fibers are present in the outer layers of the annulus fibrosus under normal conditions. Some reports have suggested that the presence of sensory nerve fibers in the deeper layer of the annulus fibrosus and the production of inflammatory mediators in the degenerated nucleus pulposus lead to disco-
genic low back pain in patients with degenerated intervertebral discs (27). Burke et al. reported that intervertebral discs from patients with discogenic low back pain contained more inflammatory mediators than did intervertebral discs from pa-

tients with intervertebral disc herniation (7). These reports strongly suggest an association between sensory nerve ingrowth, inflammatory mediators, and discogenic low back pain.

In animal models, the inflammatory mediators in the discs may promote CGRP-IR axonal ingrowth and may, at least in part, explain the mechanism of nerve ingrowth into the inner an-
nulus (20). It is also possible that nerve ingrowth is induced as a consequence of reduction of the barrier provided by proteoglycan and the human cartilage large aggregating pro-

teoglycan, aggrecan, to axonal growth after degeneration of the lumbar intervertebral discs (29,30). In fact, animal models of disc degeneration showed the induction of nerve ingrowth in association with a depletion of proteoglycan (29). Considering our present and these previous reports, ingrowth of sensory nerve fibers might be closely associated with the pathogene-

sis of discogenic low back pain.
interferon-gamma, and nitric oxide (NO) are up-regulated in herniated intervertebral discs resected during surgery. Kepler et al. has reported pain-related molecules including chemokine regulated upon activation in normal T cells, expressed, probably secreted (RANTES) and its promoter, IL-1beta, were significantly elevated in painful discs compared to painless discs. In addition, Burke et al. documented that discs from patients with low back pain produced significantly more pain-related molecules than discs from patients with sciatica. These findings suggested that there is persistent inflammation in painful discs, and that the production of these molecules may be a major factor in discogenic low back pain.

**In vivo studies**

Several animal models of intervertebral disc degeneration have been used as animal models of discogenic low back pain. Disc injury models including puncture by needles and disc stab by blade have been reported, and several pain-related molecules have been detected in the injured discs. In their study of disc puncture models in rabbits, using a 16-gauge needle, Sobajima et al. reported that disc injury induced the upregulation of IL-1 and nitric oxide synthase (iNOS) transiently (within 3 weeks). In our study using a disc puncture model, nerve growth factor and TNF-alpha levels (over 1 week) and IL-6 levels (over 4 days) were significantly increased in the injured disc, but the upregulation of these molecules resolved within 2 weeks after disc injury. This type of disc injury induces transient inflammation, but degenerated discs in humans show persistent inflammation. This discrepancy might be one of the limitations of animal models of disc injury. Several authors have attempted to solve this discrepancy between animal models and human samples. Ulrich et al. reported repeated disc injury induced inflammatory response with elevated levels of TNF-alpha, IL-1beta, and IL-8 up to 28 days after injury. Lotz et al. developed a different animal model of disc degeneration, and reported disc static compression induced disc cell death depending on the magnitude and duration of spinal loading. We modified this disc compression model and reported that the combination of disc dynamic compression and disc injury induced long-lasting upregulation of inflammatory mediators, including TNF-alpha, IL-1beta, IL-6, and NGF. This indicates that not only disc injury but also repetitive trauma or mechanical stress are important for representative animal models of disc degeneration in humans.

**In vitro studies**

Several authors have evaluated the role of pain-related molecules found in human samples or in vivo. Goupille et al. reported TNF-alpha is known to promote irreversible degradation of aggrecan; disc catabolism; and expression of inflammatory mediators and NGF. In their in vitro study, Hoyland et al. reported that IL-1beta was up-regulated in discs clinically associated with chronic low back pain and that IL-1 beta antagonists inhibited matrix degradation. They concluded that IL-1 is a key cytokine mediator in degenerated discs and therefore a therapeutic target.

**The role of immune cells**

Despite controversy surrounding which cells produce pain-related molecules, it has been reported there were several immune cells including macrophages, T-cells, B-cells, and natural killer cells in degenerated discs. In addition, inflammatory cytokines studies have reported that pain-related molecules are expressed by immune cells, including macrophages. Takata et al. demonstrated that interaction between disc tissue and macrophages is necessary for upregulation of IL-6 production. However, whether macrophages exist in normal healthly disc was still unclear. Nerklich et al. reported that the intact nucleus pulposus contains a high number of resident macrophages. On the other hand, it has been reported that the healthy normal intervertebral disc was an immunologically privileged environment. One hypothesis for the possible entry pathway of immune cells is that the injury of annulus fibrosus, the leakage of nucleus pulposus, and deep nerve and vessels ingrowth into the disc might be a trigger of immune cell supply in discs.

**Therapeutic targets for discogenic low back pain**

These inflammatory mediators are potential targets for discogenic low back pain. In a rat disc injury model, intradiscal injection of etanercept (TNF-alpha inhibitor) suppressed pain-related neuropeptide expression in DRGs innervating injured discs. Clinical studies have revealed the efficacy of these inhibitors in discogenic low back pain. Tobinick et al. reported that TNF-alpha inhibition by etanercept delivered by perispinal administration may offer clinical benefit to patients with chronic, treatment-resistant discogenic pain. Sainoh et al. reported the efficacy of etanercept and anti-IL6 antibody for disc pain patients compared to placebo. Tanezumab is a humanized monoclonal antibody that specifically inhibits nerve growth factor as a treatment for chronic pain. In a study where patients (n = 1,347) received intravenous tanezumab, naproxen, or placebo, tanezumab provided significantly greater improvement in pain, function, and global scores vs. placebo and naproxen in patients with chronic low back pain.

**Mechanical Hypermobility**

Segmental hypermobility is considered another major factor associated with discogenic low back pain. Hypermobility is induced through disc degeneration because the lumbar intervertebral discs have a major load-bearing role in humans, but disc degeneration itself is reported not to be associated with hypermobility. Of course, not all degenerated discs are symptomatic, and symptomatic and asymptomatic degenerated intervertebral discs show similar structural and biochemical features. Disc degeneration is markedly common, but a definitive and widely accepted definition remains unclear. In clinical studies using MRI, disc degenera-
tion has been suggested to be one of the most remarkable risk factors for discogenic low back pain \(^{60-65}\). Many papers identified genetic influences and unidentified factors, which include complex and unpredictable interactions for the presence of disc degeneration; besides, disc degeneration might not be induced by most environmental factors \(^{64,65}\). Even more, several mechanisms have sought to explain how degenerative changes in the disc cause pain. In 1989, Nachemson suggested in a presentation at the AAOS, that environmentally or genetically induced premature aging changes may render the disc mechanically incompetent, creating abnormal motion patterns that subject various spinal structures to undue stress, causing pain \(^{60}\).

Some studies have reported instability for mild degeneration \(^{65,66,69}\), while other studies have showed increasing spinal stiffness with progressing degeneration \(^{90,91}\). Some papers indicated that hypermobility between flexion and extension is associated with degenerative disc disease \(^{2,27}\). Fujiwara et al. evaluated 110 lumbar motion segments from 44 human cadavers, and reported that segmental motion increased with increasing severity of disc degeneration to grade IV and decreased in grade V, as classified by MRI. Also, such segmental motion changes were greater in axial rotation compared with the other motion as lateral bending, flexion and extension \(^{65}\). Tanaka et al. evaluated 114 lumbar spine segments taken from 47 fresh cadavers and suggested that lumbar spine angular mobility is related to disc degeneration, and angulation was greater in grades III and IV degeneration, in which radial tears of the annulus fibrosus are found in Thompson’s grading system \(^{95}\). Several animal studies advocated that torsional loads are important factors for the degeneration of the motion segments \(^{26-29}\). In cadaveric study, a relationship between the severity of disc degeneration and increases of the torsional movement was reported \(^{77}\). Although, it is consensus in previous papers that severe loss of height in the intervertebral disc, sclerosis in the endplate, and osteophyte formation around bone structure were induced in the final stage of disc degeneration, resulting in stabilization of the motion segments, as first reported in 1980s by Kirkaldy-Willis \(^{5,9,26-30}\).

Histologically, based on the loss of differentiation between the annulus fibrosus and nucleus pulposus, as well as changes in collagen content from Type II to Type I and decreased proteoglycan, hypermobility at the specific lumbar segment is induced by the loss of structural integrity, insufficient hydration, and the lack of tolerance against motion of lumbar spine \(^{47,53-56}\). At the next stage, decreased hydration within the nucleus pulposus results in decreased disc pressure and reduced disc height, and at that time, degeneration is characterized by a fibrotic nucleus pulposus and an annulus fibrosis with many clefts or fissures \(^{60}\). As the inner part of the annulus fibrosus increases in size and the interface between the nucleus pulposus and annulus fibrosus becomes unclear, segmental hypermobility is gradually stabilized with a disc height narrowing \(^{59}\).

To create a model of discogenic low back pain, puncture incision of discs has been widely used in various animals \(^{57,87,88}\). Using this puncture-induced discogenic low back pain model, stabilization established by lumbar posterolateral fusion, inhibited sensory nerve ingrowth into punctured intervertebral discs and upregulation of CGRP expression in DRG neurons innervating intervertebral discs in rats, suggests that stabilization itself can reduce discogenic low back pain \(^{99}\). It is still unclear how hypermobility of the segment is related to the development of discogenic low back pain, but at least, pain induced by the puncture of the intervertebral disc was suppressed by stabilization of the affected segment. This may suggest that transient or persistent inflammation in the disc, which is induced by hypermobility of the lumbar spine, is suppressed, resulting in pain relief. However, there is evidence in human studies that suggests that histomorphological features, instability of the lumbar spine, and low back pain bear no relationship to one another \(^{99}\), and that the clinical outcome of lumbar fusion surgery is highly variable \(^{99}\). This suggests that many factors, including patient selection or background, may affect the surgical outcome. Definite evidence of stabilization efficacy remains elusive. Further studies should be undertaken to shed light on the difference between symptomatic and asymptomatic degenerated discs, and the pathological mechanisms of discogenic low back pain.

### Conclusions

Animal models and samples from humans have revealed that sensory nerve innervation of lumbar intervertebral discs and increases in levels of cytokines such as TNF-alpha, interleukins, and NGF, may be accelerated by disc degeneration and hypermobility. In this regard, it is important to prevent sensitization of sensory nerve fibers innervating the disc, suppress increases of cytokines, and possibly decrease disc hypermobility for the treatment of discogenic low back pain.

### Conflicts of Interest

The authors declare no conflicts of interest with respect to the authorship and publication of this article.

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