ELSEVIER

CrossMark

The Spine Journal 15 (2015) 1347–1355

THE SPINE JOURNAL

Basic Science

Pathomechanisms of discogenic low back pain in humans and animal models

Seiji Ohtori, MD, PhD[a,*], Gen Inoue, MD, PhD[a], Masayuki Miyagi, MD[b], Kazuhisa Takahashi, MD, PhD[a]

[a]*Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan*
[b]*Department of Orthopaedic Surgery, Kitasato University, School of Medicine, 1-15-1 Kitasato, Minami, Sagamihara, Kanagawa, 252-0374, Japan*

Received 17 May 2011; revised 10 February 2013; accepted 25 July 2013

Abstract

BACKGROUND CONTEXT: Although explored in humans and animal models, the pathomechanisms of discogenic low back pain (LBP) remain unknown.
PURPOSE: The aim of this study was to review the literature about the pathomechanisms of discogenic LBP.
METHODS: Animal models of discogenic pain and specimens from degenerated human intervertebral discs (IVDs) have provided clues about the pathomechanisms of discogenic LBP. Painful discs are characterized by a confluence of innervation, inflammation, and mechanical hypermobility. These three possible mechanisms are discussed in this review.
RESULTS: Animal models and specimens from humans have revealed sensory innervation of lumbar IVDs and sensory nerve ingrowth into the inner layer of IVDs. Cytokines such as tumor necrosis factor-α and interleukins induce this ingrowth. Nerve growth factor has also been recently identified as an inducer of ingrowth. Finally, disc degeneration induces several collagenases; their action results in hypermobility and pain.
CONCLUSIONS: To treat discogenic LBP, it is important to prevent sensitization of sensory nerve fibers innervating the IVD, to suppress pathogenic increases of cytokines, and to decrease disc hypermobility.

Keywords: Intervertebral disc; Pain; Sensory nerve; Inflammation; Hypermobility; Psychosocial factors

Introduction

Low back pain (LBP) is a common clinical problem and has significant adverse socioeconomic implications. According to Nachemson [1], a singular occurrence of LBP occurs in approximately 15% to 30% of the population, the 1-month prevalence is 19% to 43% of the population, and the lifetime prevalence is as high as 60% to 80% of the population. Low back pain can be divided into either specific or nonspecific LBP. Specific LBP can be induced by obvious causes such as spinal tumors or spinal infection. However, 80% to 90% of LBP cases can be classified as nonspecific without apparent causes, and it is often chronic and can be difficult to treat.

Intervertebral discs (IVDs) have been considered to be a source of LBP. Independent studies of adult LBP patients have estimated IVD prevalence rates ranging from 39% to 42% [1,2]. This view is supported by the findings that injections of local anesthetics into damaged IVDs eliminate acute pain [3]. However, the pathophysiology of discogenic LBP is not well established [4].

Recently, studies using animal discogenic pain models and specimens from degenerated human IVDs have provided insights into the pathomechanisms of discogenic LBP. Lotz and Ulrich [5] suggested that painful discs are characterized by a confluence of innervation, inflammation, and mechanical hypermobility. This article reviews some of the basic research on discogenic LBP in humans and animal models (Figure).

FDA device/drug status: Not applicable.

Author disclosures: ***SO:*** Nothing to disclose. ***GI:*** Nothing to disclose. ***MM:*** Nothing to disclose. ***KT:*** Nothing to disclose.

SO, GI, and MM contributed equally to this work.

The authors did not receive and will not receive any benefits or funding from any commercial party related directly or indirectly to the subject of this article.

* Corresponding author. Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. Tel.: (81) 43-226-2117; fax: (81) 43-226-2116.

E-mail address: sohtori@faculty.chiba-u.jp (S. Ohtori)

1529-9430/$ - see front matter
http://dx.doi.org/10.1016/j.spinee.2013.07.490

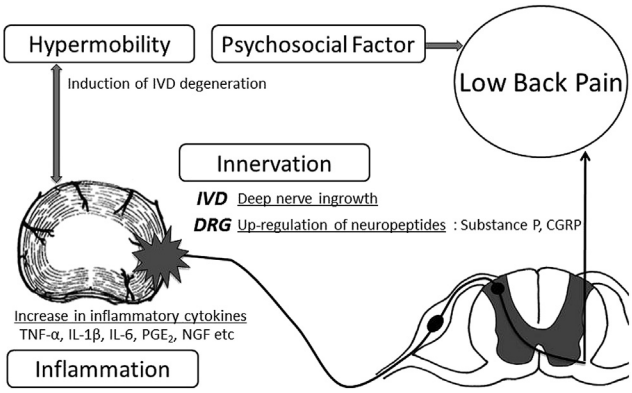

Figure. Pathomechanisms of discogenic low back pain (LBP). Innervation: animal model and specimens from humans revealed sensory nerve innervation of lumbar intervertebral discs (IVDs) and sensory nerve ingrowth into the inner layer (deep nerve ingrowth) of the degenerated IVD. Lower IVDs are thought to be innervated multisegmentally by dorsal root ganglia (DRGs). DRG neurons innervating IVDs may be primarily involved in pain perception related to inflammatory pain by neuropeptide-containing neurons such as substance P and CGRP. Inflammation: many researchers have identified various proinflammatory molecules, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, prostaglandin E_2 (PGE_2), and nerve growth factor (NGF) in IVDs of various animal discogenic pain models and human degenerated IVD specimens. Hypermobility: hypermobility of motion segment is usually induced in degenerated IVD. In addition, disc degeneration induces several collagenases, thereby resulting in hypermobility and pain. Psychosocial factors: psychosocial factors are reported not only to give rise to LBP but also to prolong LBP from the acute phase to the chronic phase. These factors are thought to be the major factors that induce discogenic LBP.

Sensory innervation

Sensory nerves in IVDs

Since the first description of the sinuvertebral nerve by Luschka [7], many investigators have reported that the lumbar IVD is innervated by sinuvertebral nerves consisting of spinal sensory and postganglionic sympathetic fibers and that the disc is segmentally innervated by sensory nerves in animals and humans [5,8–13]. Whether nerve endings are present within IVDs is controversial. Some investigators disagree with the notion that nerve endings are present in the IVD and thereby deny the possibility of pain originating from the discs themselves [14–16]. However, other studies have demonstrated nerve endings in the annulus fibrosus in humans [17–20].

Immunohistochemical studies have revealed molecular characteristics of nerve fibers innervating the IVD. Protein-gene product 9.5 [21,22], substance P (SP) [23,24], calcitonin gene–related peptide (CGRP) [21,25,26], dopamine β-hydroxylase [26], vasoactive intestinal polypeptide [26,27], neuropeptide Y [22,27], and tyrosine hydroxylase [27] immunoreactive nerve fibers have been reported to be present within lumbar IVDs in humans. Protein-gene product 9.5 is a general neuronal marker; SP and CGRP are sensory nerve markers associated with pain; and dopamine β-hydroxylase, neuropeptide Y, and tyrosine hydroxylase are noradrenergic sympathetic postganglionic nerve fiber markers expressed in peripheral nerves. Vasoactive intestinal polypeptide is located primarily in nerves originating from postganglionic sympathetic and parasympathetic neurons but is sometimes located in dorsal root ganglia (DRGs) neurons. Therefore, lumbar IVDs are thought to receive nerve fibers from DRGs, sympathetic ganglia, and parasympathetic ganglia.

Sensory neurons involved in pain perception related to inflammatory pain are typically small nerve growth factor (NGF)–dependent peptide-containing neurons that are immunoreactive for SP and CGRP. Small non–peptide-containing neurons that bind isolectin B4 (IB4) from *Griffonia simplicifolia* have also been suggested to be involved in various pain states, such as neuropathic pain from injured nerves. Some reports have indicated that the proportion of IB4-binding neurons innervating skin is higher than that of CGRP-binding neurons [28,29]. In contrast, the proportions of IB4-binding and SP-immunoreactive (IR) DRG neurons innervating the rat lumbar disc have been reported to be 0.6% and 44%, respectively [30]. In humans, CGRP-IR nerve fibers, but not IB4-binding nerve fibers, are present in lumbar IVDs [31]. These findings suggest that sensory nerve fibers innervating IVDs are primarily involved in pain perception related to inflammatory pain transmission by NGF-dependent peptide-containing neurons.

Sensory pathways from IVDs to the spinal cord

Patients with degenerated lumbar IVDs in the lower segments (L4–L5 or L5–S1) occasionally report groin pain [32,33]. Furthermore, individuals who undergo percutaneous disc surgery performed under local cutaneous anesthesia sometimes report groin pain when the lateral side of the disc is pierced by a probe [33]. The groin area is innervated by the genitofemoral and ilioinguinal nerves, which are terminal branches of the L1 or L2 spinal nerves. Groin pain, therefore, is considered to be referred pain that is distinct from the nerve root pain caused by IVDs. Takahashi et al. [34] have reported direct evidence for groin pain referred from IVDs: administration of capsaicin into the anterior portion of a lumbar IVD of rats pretreated with Evans blue (intravenously) caused dye extravasation in the groin skin and suggested the presence of dichotomizing sensory C-fibers that innervate both the IVDs and the groin skin. In rats, sensory nerve fibers from the lower IVD are thought to be innervated by DRGs at the corresponding level and multisegmentally by DRGs at upper levels [35–37]. In the nonsegmental innervation, sensory nerve fibers are thought to enter the paravertebral sympathetic trunks and reach the L2 DRGs [35–37].

Nakamura et al. [38] performed an L2 spinal nerve block based on animal sensory innervation and reported that the block was effective in patients suffering from discogenic LBP. However, these researchers diagnosed discogenic LBP only by physical examination, plain X-ray films, and magnetic resonance imaging. L2 spinal nerve infiltration