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Overview

Immunobiological aspects of acute discogenic pain of low back pain

BRANKO UHODA

Specialist Hospital for Orthopaedics
Zadarska 62
23210 Biograd na moru
Croatia
E-mail: ortrav@email.t-com.hr

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INTRODUCTION

Low back pain is the most common health problem for individuals between the ages of 20 and 50 years. In most cases, the origin of low back pain remains unsolved. Many of established anatomic causes of low back pain are believed to arise from damage of the intervertebral disc (IVD) indirectly through degeneration. Although causal relationship between disc degeneration and low back pain is not yet definitive, in some cases, pathogenetic mechanisms have been elucidated. For example, Moran and King *(1)* showed that spinal instability was one of the most common causes of low back pain, and other studies have shown that the degenerative process in discs is characterized by instability, especially in traumatic pathology.

Although disc degeneration is of great clinical importance, much remains unknown about its etiology and pathogenesis. Conditions that cause degradation of nuclear and annular material properties and hence the load bearing properties of the disc may lead to damage of other spinal structures, resulting in disc collapse, herniation or spondylosis. Among the many suspected conditions such as mechanical factors, genetics, and systemic factors, insufficient nutrition of the disc has been suspected as the underlying factor in disc degeneration *(2, 8)*.

Nutrition and metabolism of intervertebral disc

The adult human disc is the largest avascular structure in the body. In adult discs, some cells may be as much as 6 to 8 mm from the nearest blood supply, which resides in the osseous endplate of the adjacent vertebral bodies. The vertebral endplate is covered by a thin layer of hyaline cartilage, the cartilaginous endplate, the deep calcified layer, and the underlying subchondral bone. The mineralized portion of endplate is penetrated by marrow contact channels (MCC), through which capillary buds emerge. These capillary buds connect the trabecular spaces to the cartilaginous endplate, but do not penetrate into it. In addition to the endplate, there is also a vascular network in the outer anulus. Several studies have demonstrated that the central region of the endplate is the predominant route of transport for metabolic processes of the disc *(2, 39, 41)*.

The actual complex transport mechanisms of disc nutrition and metabolism have also been studied. For small solutes, diffusion is the predominant molecular transport mechanism from the endplate to the nucleus. It is sufficient for transport rates consistent with the metabolic needs of the disc. Beacuse of the poroelastic nature of the disc matrix, fluid flow is inextricably coupled to the diurnal volume change in the

disc. This cyclic flow of fluid, exudation and imbibition, occurs mainly through the MCCs of endplates. Hence, for small solutes, diffusion may still predominate, but transport of larger solutes such as proteins are believed to be significantly facilitated by the bulk flow of fluid.

Nevertheless, whether the diffusion alone or in combination with convection, the predominant transport route for nutrients and metabolites in the disc remains through the endplates. Interestingly, endplate blood vessels have beeen observed to diminish after the first decade of life when the first signs of disc degeneration are evident. Also, reduced permeability of endplates is generally seen in association with disc degeneration and age-related changes. Both of these may be due to calcification of the endplates and occlusion of the MMCs observed with desease and age.

The intervertebral disc is avascular, and there are thus steep gradients in concentration of nutrients and metabolites from the blood supply at the discs' margins and to the cells in the center of the disc. Even in normal healthy animal discs, low oxygen and high lactic acid concentration (and thus acidic pH levels) compared to levels in the plasma have been measured. These gradients form when the cells use nutrients and produce metabolites at rates that are high compared to rates of transport into the disc and diffusion through the tissue. The actual concentrations of glucose, oxygen, and lactic acid in the disc will thus depend both on parameters affecting nutrient transport and on cellular metabolic rates.

Local concentrations of extracellular nutrients and metabolites are known to have a significant effect on the activity and survival of disc cells in vitro. However, using currently available techniques, measurement of these concentrations is invasive. Although measurements have been made in animal discs and in pathologic human discs during surgical procedures, such measurements cannot be carried out *in vivo* in normal human discs. Information on actual concentrations of nutrients and metabolites in disc can thus only be obtained from information on factor(s) regulating their concentrations gradients, namely transport into the disc and cellular metabolism *(38, 39, 40)*.

There have been a number of studies on factors that affect transport into the disc and through the disc matrix. From these studies, it is clear that nutrient supply to the disc can be compromised by a decrease in the blood supply to the disc, by osteonecrosis, and by calcification of the cartilaginous endplate. Such changes can produce a measurable loss in nutrient supply and hence are strongly implicated in the etiology of disc degeneration. However, local nutrient concentrations are also strongly regulated by cellular demand : in a „dead« disc, there are no nutrient gradients, and the concentrations across the disc reach those of surrounding plasma *(2,4, 39)*.

Far less is known about nutrient demand and metabolite production than about nutrient supply. There are only two studies to our knowledge that have investigated the rates of oxygen and glucose consumption and lactic acid production by the disc. Both of these studies were on disc explants and examined changes in oxygen consumption and lactic acid production as a function of oxygen tension at constant glucose and ph levels. However, such studies do not give information about physiologic conditionss in the disc, because changes in concentration cannot occur independently *in vivo*. Disc cells use glucose to produce adenosine triphosphate (ATP), with lactic acid as the resulting metabolite; the concentrations of glucose and lactic acid are thus necessarily coupled, as are oxygen and lactic acid. The center of the disc thus experiences low oxygen concentrations together with low glucose and high lactic acid concentrations (and hence acidic levels of pH). At present, it is not known how such a microenviroment will affect cellular metabolism; but the center of the disc appears most voulnerable to changes in nutrient concentrations and experiences the first signs of degeneration and death. It is thus of importance to understand disc cell metabolism and activity under such conditions *(39, 40)*.

Pathophysiological mechanisms of chronic spinal pain sindromes

The initial mechanical injury caused by abnormal motions or loads to neural tissue initiate a complicated cascade of interrelated events inducing structural tissue changes such as swelling,oedema and local cellular infiltration.

Local inflammation may induce neural structural changes that may in turn be directly responsible for modulating local electrical changes in the neural tissue.
Furthermore, a neuroimmune response is mounted in

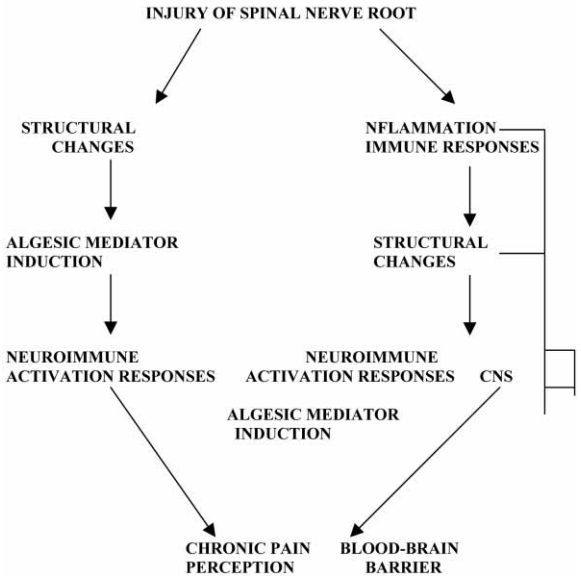

Figure 1. *Schematic diagram of the conceptual model of events at injury and afterward that lead to chronic pain. Biomechanical and physiologic responses, as important contributors in this complex cascade of events, have complicated relations with each other and final pathway that elicits pain.*

the spinal cord, where neurons and glia cells may produce a number of proinflammatory cytokines, which can in turn induce the expression of numerous algesic mediators that lead to enchanced nociceptive activity, and thus pain. In conjuction with the activation of these cells, cellular adhesion molecules are upregulated and periferal T cells and macrophages infiltrate across the blood-brain barrier into parenchyma of the spinal cord. This neuro inflammatory response can itself also enhance the neuroimmune activation response of the CNS and provide enhancement of algesic mediator production. It is important to recognize also that these CNS changes are transmitted to the brain. Affecting supraspinal pain mechanisms, the perception of chronic pain itself may play role in feeding back on the nociceptive responses *(26, 27, 28, 33)*.

Immunologically mediated pathology of intervertebral disc tissue spinal pathology

The intervertebral disc has traditionally been regarded as biomechanically important structure in the spine, with characteristic biomechanical properties related to both the annulus fibrosus and the nucleus pulposus. However, research performed mainly during the last 15 years has revealed that the intervertebral disc cells is also biologically active, and that disc degeneration and herniation is associated with the production of such as pro-inflammatory cytokines *(32, 33)*.

In the disc tissue several inflammatory mediators are produced such as phospholypase, A-2, cyclooxygenase (COX-2), prostaglandine E-2, Tumor, necrosis factor-alpha, nitric oxyde, interleukine-1 alpha, interleukine-1 beta, IL-6, IL-8 and the macrophage infiltration into protruded disc material can be the trigger for cytokine production and for continuation of neurological simptoms *(19, 25, 34, 35, 36)*.

However, certain degrees and certain phase(s) modulating immunologically the process of inflammatory cascade of spinal nerves are accompanied by various degrees of vascularisation conditioned by toxic content of degenerative disc tissue in epidural space, and by hyperalgesia *(37)*.

Role of cytokines

It has been shown that herniated cervical and lumbar disc specimens spontaneously produce increased amounts of various substances, such as nitric oxide, interleukin-6, prostaglandin E2 and certain matrix metalloproteinases. Futhermore, the cells of intervertebral discs increase their production in vitro in these substances even more when stimulated by interleukin-1 beta. Increased levels of interleukin-6 and interleukin-8 have been found in disc specimens from patients with discogenic low back pain, indicating a possible role of such substances in the pathogenesis of low back pain. Increased levels of pro-inflammatory cytokines, such as interleukin-1 beta, have been found in fact joint tissues in patients undergoing surgery for lumbar spinal stenosis and disc herniation. These observations suggest the involvement of pro-inflammatory cytokines in degenerated lumbar facet joints regarding the genesis of pain production.

In addition,i ntervertebral discs may injure spinal nerve roots not only by mechanical deformation but also by the presence of nucleus pulposus tissue in the epidural space.

Olmarker and coleagues 1993 *(20)* demonstrated that autologuos nuclus pulposus induced histologic and functional changes in spinal nerve roots with no mechanical--compressive components *(21)*. These nonmechanical effects have recently been attributed to cytokines related to intervertebral disc cells. One cytokine in particular that has been suggested to be of major importance in this context is tumor necrosis factor-alpha (TNF-alpha) *(42)*.

TNF-alpha as key player in the initiation processes of the nucleuss pulposus induced nerve root injury has been suggested to play a key role in mediating sensitization, as well as other nucleus pulposus-induced effects, such asintravascular coagulation of spinal nervespinal root and dorsal ganglion oedema (DRG) blood flow reduction through spinal nerves and damage of myelin capsule *(13)*. TNF-alfa is known to be produced and realeased from the chondtocyte-like cells of the nucleus pulposus *(13, 42)*.

Howewver, other cytokines such as interleukin-1 beta and interferon-gamma have also been suggested to be involved because of their known neurotoxic properties and their presence in the disc cells. Moreover, local application of nucleus pulposus in experimental animals may also induce a characteristic »Inflammatory crescent«, providing histologic confirmation of inflammatory reaction at the surface of dorsal root ganglion (DRG) *(13, 20, 21, 22, 36)*.

Finally, it has been suggested that intervertebral disc may be invaded by newly formed blood vessels and nerve fibers following injury of the anulus fibrosus. The nerve fibers have been considered to induce low back pain. It seems that bioactive substances within the nucleus pulposus may be involved in the induction of a neovascularisation and neoinervation. Such ingrowth seems to be reduced by Doxycycline, Infliximab and Dexamethason, cytokine inhibitors *(21, 22, 23, 25)*.

Findings have shown that intervertebral disc degeneration. alo relates to a multitude of factors, among them cytokine-induced increased production of matrix metalloproteinases, a mechanism supported by an observed correlation between the levels of matrix metalloproteinases 2 and 9 and the grade of disc degeneration. initiate intervertebral disc degeneration. In addition, recently, genetic mechanisms underlying disc degeneration have been also identified *(3, 4)*.

To conclude, the pathophysiology of sciatic pain in association with disc herniation has been shown to be related to a combination of biochemical nerve root irritat-

tion via pro-inflammatory cytokines, produced by nucleus pulposus cells and mechanical nerve root compression. The cytokine mediated nerve root inflammation induces a sensitization of nerve root so that mechanical nerve root compression leads to radiating sciatic pain. Animal experimental studies have shown that anti-TNF substances, e.g. infliximab and etanercept, can reduce or prevent TNF induced nerve root changes as well as pain behavioural reactions. Recent clinical studies have also shown positive results, indicating a possible role of anti--TNF treatment in patients with lumbar disc herniation and sciatica *(19, 20, 21)*. Evidently, there is a large body of evidence indicating that pro-inflammatory cytokines and other related substances play important roles in the pathophysiology of various spinal pain conditions.

Role of complement membrane attack complexes

At the tissue level, apoptotic disc cells were identified in samples from anulus fibrosus, particularly in discs from older subjects. Moreover, Lotz *et al.* noted an increasing number of such apoptotic disc cells with increasing compressive stress in mouse tail discs *(2)*.

Several recent studies have supported the concept of antibody-mediated mechanisms in disc patophysiology, as suggested by the biochemical demonstration of immunoglobulins, and immunoglobulin complexes have been demonstrated by immunohistochemical methods in disc herniation (DH) tissues. Notably, such immune complexes have been never observed in control disc tissue samples. Immunoglobulin-antigen complexes have been observed around nucleus pulposus cells, and possibly in newly formed blood vessels within DH tissue. The role of such immune complexes in disc tissue patophysiology remained unclear, however *(8, 9, 10)*.

Among the three pathways of complement activation, the so-called classic pathway is activated by antigen-antibody complexes, whereas complement can be also activated altenatively by either microbial cell walls or the lectin pathway, in which microbial carbohidrates interact with mannose-binding protein in the plasma.

As final step in the classic pathway activation, several complement components (C5b, C6, C7, C8, C9) form a membrane attack complex (MAC) that can destroy cells by perforating their membranes. There currently is no conclusive evidence of microbial involvement in intervertebral disc degeneration or herniated disc, but there is indirect evidence suggesting a possibility of complement activation through the classic pathway mediated by immune (antigen-antibody) complexes. In particular, immune complexes juxtaposed with disc cells have been reported. Thus it was pertinent to look for the possibility of a complement-mediated pathway of disc cell destruction, and to determine whether such complement activation, if demonstrated, applies only to pathologic disc tissues *(10, 11, 12, 14, 15, 16)*.

Pharmacotherapy of acute discogenic pain

Nonspecific cytokine inhibition

Anti-inflammatory cytokine therapy may become an effective treatment of sciatica due to disc herniation. Major advancement in the management of „discogenic« back pain will depend upon an appreciation of the importance of controlling neural inflammation in the early phases of the desease rather than developing new techniques of managing irreversible neural lesions and their iatrogenetic sequelae. The pain may occur as a result of compression of adjacent neural structures as well as by realease of irritating chemicals.

In selected cases immediate relief from pain occurs after administration of anti-TNF-alpha medication. The important point is that with development of intraneural fibrosis the abnormalities become irreversibile and at our present knowledge untreatable.

Thus, the early treatment of low back pain might prevent future development of irreversible local changes.

In approach to the problem of a syndrome acute low back pain due to disc pathology an attempt was made to combine therapeutical protocole for „ Acute disc sindrom« and in combination with a coctail of **Corticosteroids** (by direct inhibition of the expression of leukocite adhesive molecules and suppression of synthesis of cytokines and blocking the initial steps in receptive transduction of signals into cell), and indirectly-induction of syntesis of macrocortine (**Lipomoduline)** which inhibits activation of phospholipase A2 and creating eicosanide by blocking the initial steps in receptive transduction of signals into cell. **Diuretics, (**by preventing i.e. reduce spinal root and dorsal ganlion oedema), **Doxycycline**, (blocking the activity of TNF-alpha) *(42)* **Indomethacin** i.e. **Pyroxicame** as equivalent to Indomethacin (by inhibition to neutrofile activation).

Although in recent literature there have been quoted about the attempts of tretment of acute ischiatic pain by use of selective monoclonal inhibition (Infliximab), we consider that it is still not applicable in clinical praxis because of complexity of immunological reaction, pleotropism of citokyne actions and so far with its of toxicity and side-effects *(34)*.

In conclusion, injury to nerve roots causes profound changes in input from primary afferents innervating the dorsal horn.

Early and timely applicated farmacotherapy in acute phase of discogenic pain of spine, from a few hours to few days after the injury will prevent the development of syndrome of chronic spinal pain, which may end up with invalidity and suffer for millions in the world.

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