Review

Pathophysiology of disk-related sciatica.
I.—Evidence supporting a chemical component

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Abstract

Sciatica in patients with disk disease was long ascribed to pressure put on the sciatic nerve root by a herniated disk. However, a role for chemical factors acting in conjunction with this mechanical insult is suggested by a number of clinical observations: disk surgery does not consistently provide pain relief, large disk herniations are not always symptomatic, severe pain may be present in patients without imaging evidence of nerve root compression, the severity of symptoms and neurological signs is not well correlated with the size of the disk herniation, and conservative therapy is often effective. Experimental studies have provided further evidence for a chemical component: disk herniations can undergo spontaneous resorption, the intervertebral disk is immunogenic, and mediators for inflammation have been identified within intervertebral disk tissue.

The current pathophysiological theory incriminates proinflammatory substances secreted by the nucleus pulposus (NP). When preexisting or concomitant mechanical injury to a nerve root occurs, these substances can cause nerve root pain. Animal experiments have established that the NP can induce functional and structural nerve root abnormalities in the absence of mechanical compression and that this effect is mediated by substances located at the surface of NP cells. Methylprednisolone, diclofenac, indomethacin, doxycycline, and cyclosporine induce variable inhibition of this effect. Available information points to tumor necrosis factor-α (TNF-α) as the main candidate among substances potentially responsible for nerve root pain. Therefore, trials of TNF-α antagonists in patients with disk-related sciatica are warranted.

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Keywords: Disk-related sciatica; Nucleus pulposus; Mechanical compression; Chemically induced pain; TNF-α

1. Introduction

TNF-α antagonists are being investigated as new treatment tools for disk-related sciatica [1,2]. Data from clinical observations, animal experiments, and human studies suggest that they may be effective in this indication. A review of these data are timely.

2. Pathophysiology of disk-related sciatica

In 1934, Mixter and Barr [3] showed that sciatica was associated with disk herniation. Disk-related sciatica was therefore ascribed to compression of the nerve root by a herniated disk. As a result, surgical treatment to lift the compression became the treatment of reference for patients with refractory sciatica. However, recent data have established that sciatica is due not only to mechanical injury, but also to chemical inflammatory factors.

2.1. Clinical observations

Clinical arguments supporting a role for compression include the common finding upon surgery of root displacement or lamination by herniated disk material, the effectiveness of surgery in patients whose clinical manifestations are consistent with imaging findings, and the immediate postoperative pain relief noted in many patients. Many clinical observations argue in favor of a role for chemical factors, however.
Surgery to relieve nerve root compression is not consistently successful, regardless of the technique used [4]; although short-term success rates are high, in the 80–90% range, a detailed analysis of long-term success rates shows lower values ranging from 40% to 80% [5–13]. In a retrospective study by Loupasis et al. [5] of 109 patients with a mean follow-up of 12.2 years (7–20 years), more than one third of the patients were dissatisfied with the surgical procedure. Yorimitsu et al. [9] retrospectively studied 72 patients followed up for more than 10 years and noted residual low back pain in three fourths of patients and persistent nerve root pain in over half the patients. In the prospective study by Asch et al. [12] of 212 patients followed up for only 2 years, 80% of patients were free of nerve root pain, 77% were free of low back pain, and 76% were satisfied with the surgery; however, only 65% of patients had returned to their usual everyday activities and 61% to work. Reoperation rates have varied across series from 5% to 25% [6,13–17].

Large disk herniations may cause no symptoms [18–20], and on the other hand, some patients with severe symptoms have no evidence of nerve root compression upon imaging studies [21–23]. Furthermore, the severity of symptoms and neurological abnormalities is not well correlated with the size of the herniation [24–26]. Imaging features of the disk herniation have little prognostic value [27,28]. Conservative treatment is often effective, despite persistence of the disk herniation. Surgery and conservative treatment have produced similar 12-month results, even in patients with neurological abnormalities ranging from 40% to 80% [5–13]. In a retrospective study of 12.2 years (7–20 years), more than one third of the patients were dissatisfied with the surgical procedure. Yorimitsu et al. [9] retrospectively studied 72 patients followed up for more than 10 years and noted residual low back pain in three fourths of patients and persistent nerve root pain in over half the patients. In the prospective study by Asch et al. [12] of 212 patients followed up for only 2 years, 80% of patients were free of nerve root pain, 77% were free of low back pain, and 76% were satisfied with the surgery; however, only 65% of patients had returned to their usual everyday activities and 61% to work. Reoperation rates have varied across series from 5% to 25% [6,13–17].

2.2. Experimental studies

A large body of experimental data supports a role for chemical factors. Studies involving serial computed tomography (CT) or magnetic resonance imaging (MRI) documented spontaneous resorption of herniated disks, which was more marked in patients with large or sequestered herniations [35]. Both metalloproteases released by macrophages and neovascularization induced by angiogenesis factors contribute to disk resorption [36–38].

That the intervertebral disk is immunogenic has been convincingly established [39–42]. After embryonic development is complete, the vessel-free nucleus pulposus (NP) receives no exposure to the immune system. Herniated disk material, particularly when sequestered, may release substances capable of inducing an autoimmune response, which in turn may generate a chronic inflammatory response [43–45]. NP from animals and humans has been found antigenic [46], and antibodies to NP have been detected in serum from human patients and animal models [41,43,46]. For instance, epidural injections of NP in dogs induced an inflammatory response with granuloma development [42]. Autoantibody formation was detected in rabbits given injections of NP [43]. In pigs, NP was found to have chemotactic effects responsible for vascular thrombosis [47]. Inflammation mediators (phospholipase A 2, prostaglandin E 2, interleukin (IL)-1a, IL-1β, IL-6, tumor necrosis factor [TNF]-α, and nitric oxide [NO]) have been identified in and around the intervertebral disk in numerous in vitro and in vivo studies [48–53]. These mediators stimulate the release of metalloproteases, which play a pivotal role in disk degeneration [54].

Compelling evidence from animal models shows that nerve root compression is not sufficient to cause nerve root pain [55,56]. Mechanical compression of a healthy nerve root caused dysesthesia, paresthesia, or motor loss, but no pain. In volunteers who underwent disk surgery under local anesthe-sia, moderate mechanical stimulation of a nerve root having no contact with the herniated disk merely caused discomfort, whereas the same stimulation applied to a nerve root in contact with a disk herniation often replicated the sciatica [56]. To investigate chemical factors, Olmarker et al. [39] developed a pig model in which NP or retroperitoneal fat (as a control) is introduced within the epidural space, at a distance from the nerve roots. Alterations in nerve conduction velocity (NCV) were noted after 1–7 days, as well as focal histological changes denoting nerve fiber degeneration. Two hypotheses were put forward to explain these changes: release by the NP of substances having direct effects on nerve fibers, and an inflammatory or vascular response [39]. This study provided the first evidence that NP can induce nerve root damage in the absence of compression, a fact that strongly suggested a role for chemical factors.

Although chemical factors have been extensively studied in recent years, disk-related sciatica does not occur in the absence of mechanical compression [57–61]. Several groups investigated the roles for mechanical nerve fiber compres-
sion and for chemical factors, acting alone or in combination. Although the findings are partly contradictory, they shed light on the pathophysiology of disk-related sciatica [62–68]. In the pig model developed by Cornefjord et al. [62], the morphological and functional changes induced by NP, mechanical compression, or both were compared. Application of NP or nerve root compression was followed by a decrease in NCV, and the effect of combining these two insults was not greater than the effect of each insult alone. After NP application, the contralateral nerve root serving as the control also exhibited a reduction in NCV. Histological axon abnormalities occurred only after mechanical compression, indicating that they probably did not cause the NCV decrease. A rat model of experimental disk herniation followed by videotape recording to evaluate pain-related behaviors was developed [63]. Four groups of 10 rats were studied: a control group, a group subjected to disk incision, a group subjected to nerve root displacement (displacement of the L4 dorsal ganglion and stretching of the L4 root), and a group subjected to both insults. Behavioral disorders occurred only in the group with both disk incision and nerve root displacement, leading the authors to conclude that both a chemical and a mechanical factor were needed [63]. In another experimental study, 18 dogs were separated in four groups: controls, NP application without compression, chronic compression, and both NP application and chronic compression [64]. Effects were assessed by electrophysiology (reduction in NCV) and histology (intraneural edema, Schwann cell edema, and nerve fiber damage). Abnormalities were more severe in animals subjected to both insults. An experimental study in rats established that hyperalgesia after NP application was more severe and more long-lasting when the nerve was previously subjected to chronic mechanical compression [65]. In another study, 51 rats were separated into six groups, as follows: compression by a disk; compression not due to a disk; introduction of disk, NP, or anulus fibrosus into the epidural space without compression; and no intervention (controls) [66]. Animals in all five intervention groups showed evidence of prolonged hyperalgesia. Pain severity was greatest and time to pain onset shortest in the disk compression group. Thus the findings indicate that both mechanical and chemical factors contribute to the pathogenesis of disk-related sciatica and that, when present in combination, these factors probably exert a synergistic, rather than an additive, effect. More importantly, this study suggests that chemical factors may play the predominant role early in the pathogenic process. Similarly, effects were more severe when compression and NP application were combined in a rat model used to evaluate the production of nerve growth factor, a potential source of hyperalgesia and neuropathic pain [67]. In another experiment, NP application combined with root displacement, but not either factor alone, decreased the thermal stimulation threshold, leading to hyperalgesia [68]. The authors concluded from this finding that both a mechanical factor and chemical irritation were needed to induce pain.

2.3. Theory based on clinical and experimental data

Although at times contradictory and difficult to interpret, clinical and experimental data support the following conclusions: even in the absence of mechanical compression, substances produced by the NP can induce functional and structural nerve root abnormalities; nevertheless, pain seems to occur only when a previous or concomitant mechanical insult is present.

3. Animal models used to identify chemical factors produced by the nucleus pulposus

Olmarker and Rydevik conducted landmark studies in this area. Their Swedish research group used a rigorous scientific approach leading from clinical observations started over 10 years ago in humans to experimental studies suggesting a role for TNF in the pathogenesis of nerve root pain (Fig. 1), then to studies establishing that TNF-α antagonists were effective in animals and, finally, to a randomized controlled study in humans.

3.1. Hypothesis that the nucleus pulposus secretes chemical factors

Involvement of a chemical component was confirmed in the pig model developed by Olmarker et al. [39]. Six groups of five animals (n = 30 in all) were used. Either NP or retroperitoneal fat as a control was introduced into the epidural space, without mechanical compression. As compared to the control, NP induced NCV abnormalities within 1–7 days, as well as focal histological changes [39]. The NCV reduction was significant as early as day 1 and was more marked at the two subsequent time points (days 3 and 7) (Table 1). Histology showed similar numbers of leukocytes and macrophages

![Diagram](image-url)
Table 1

<table>
<thead>
<tr>
<th>Day</th>
<th>Fat</th>
<th>Nucleus pulposus</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>82 ± 4</td>
<td>63 ± 9*</td>
</tr>
<tr>
<td>Day 3</td>
<td>83 ± 4</td>
<td>45 ± 16*</td>
</tr>
<tr>
<td>Day 7</td>
<td>76 ± 11</td>
<td>45 ± 19**</td>
</tr>
</tbody>
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*P < 0.01; **P < 0.05.

Table 2

<table>
<thead>
<tr>
<th>NP</th>
<th>NP + MP 5 min</th>
<th>NP + MP 24 h</th>
<th>NP + MP 48 h</th>
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<tbody>
<tr>
<td>NCV (m/s)</td>
<td>23 ± 16*</td>
<td>75 ± 13**</td>
<td>76 ± 8**</td>
</tr>
</tbody>
</table>

***P < 0.001 and ****P < 0.01 versus the NP.

* Compare to the control group value (76 ± 11 m/s) in the previous study by Olmarker et al. [56].

Changes in nerve conduction velocity (m/s) after application of nucleus pulposus (NP) or retroperitoneal fat in 30 pigs. From Olmarker et al. [39].

3.2. Effects of antiinflammatory treatments

Under the hypothesis that inflammation may contribute to the pathogenesis of sciatica, the effects of antiinflammatory drugs were investigated in animal models. Resolution of previously documented abnormalities after antiinflammatory therapy would constitute indirect evidence supporting a role for proinflammatory factors. The above-described pig model was used. Pretreatment or early treatment with high-dose methylprednisolone restored normal nerve conduction velocity [69]. In 20 pigs, NP was introduced into the epidural space; five animals served as controls and three groups of five animals received high-dose (30 mg/kg) methylprednisolone 5 min, 24, and 48 h later, respectively. Electrophysiological testing and histological studies were conducted on day 7. NCV decreased after NP application but returned to normal after methylprednisolone injection 5 min and 24 h later; a smaller improvement was noted in the group treated after 48 h (Table 2). Histology showed no differences across the four groups regarding inflammatory cells or nerve fiber alterations. Another study in the same model investigated the effects of corticosteroid therapy on increased endoneurial vascular permeability induced by NP in the same model [70]. NP was introduced into the epidural space in 20 pigs, of which eight received 30 mg/kg of methylprednisolone and 12 the same volume of saline; the control group was composed of five pigs subjected to application of retroperitoneal fat. Fluorescent albumin was injected intravenously 2 h later, and endoneurial extravasation of labeled albumin was assessed under an ultraviolet microscope. This assessment was consistently negative in the controls. After NP applications, endoneurial albumin extravasation was noted in 67% of untreated animals and 25% of treated animals. The effects of the nonsteroidal antiinflammatory agents diclofenac and ketoprofen were evaluated in the same model [71]. Three groups of six pigs received daily injections of diclofenac (3 mg/kg), ketoprofen (4 mg/kg), or saline, for 7 days. NCV was significantly higher in the diclofenac group than in the saline group (57 ± 6 vs. 38 ± 18 m/s; P < 0.05); with ketoprofen, the increase was not statistically significant (42 ± 24 m/s). The difference between diclofenac and ketoprofen is difficult to interpret. This study shows that abnormal NCVs can be corrected by nonsteroidal antiinflammatory drug therapy. Interestingly, in an animal model of chronic nerve compression, diclofenac or ketoprofen therapy resulted in better NCV results, as compared to saline [72]. In a rat model, the hyperalgesia induced by NP application without mechanical compression improved after epidural injection of cyclooxygenase-2 inhibitors [73]. In another experimental model, disk herniation was produced by incision of the L6-L7 disk in dogs. No mechanical compression was used. Of the 41 dogs included in the study, 26 underwent disk incision followed by indomethacin (n = 12, 5 mg/kg orally for 6 days) or no treatment (n = 14); among the 15 dogs not subjected to disk incision, five did and 10 did not receive indomethacin. NCV and intraneural blood flow were measured on day 7 [74]; in keeping with previous experiments, disk incision was followed by reductions in NCVs and intraneural blood flow, and these abnormalities were corrected when indomethacin was given concomitantly.

Taken in concert, these animal experiments support a proinflammatory effect of NP factors capable of causing electrophysiological abnormalities.

3.3. Source of substances contributing to nerve root pain

To identify the source of proinflammatory factors released by the NP, NCVs were measured after application of untreated NP (n = 2) or of NP previously exposed to 37 °C for 24 h (n = 5), –20 °C for 24 h (n = 5), or hyaluronidase digestion for 24 h (n = 6) [75]. NCVs were reduced in the 37 °C and hyaluronidase group, but not in the –20 °C group, as compared to the control (Table 3). Exposure to –20 °C caused extensive cell lysis (affecting more than 90% of cells, as compared to less than 5% in the other groups), strongly suggesting that NP cells released the chemical factors impairing NCVs [75]. The effects of cultured NP cells on NCV were therefore investigated [76]. The results identified the cell sur-

Table 3

<table>
<thead>
<tr>
<th>NP at 37 °C</th>
<th>NP at –20 °C</th>
<th>NP digested by hyaluronidase</th>
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<tbody>
<tr>
<td>NCV (m/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44 ± 3</td>
<td>40 ± 10</td>
<td>74 ± 9*</td>
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</table>

*P < 0.001 versus the other nucleus pulposus conditions.
face as the most likely source of offending chemical factors [76]. In the same model, autologous NP cells or fibroblasts were cultured; culture medium (possibly containing chemicals released by the cells) was injected to five animals, killed fibroblasts to four animals, live fibroblasts to five animals, killed NP cells to five animals, and live NP cells to five animals. NCVs on day 7 were unchanged in the groups given culture medium, killed fibroblasts, or live fibroblasts but were decreased in the groups given killed or live NP cells (Table 4) [76]. Although difficult to interpret, these results are consistent with activation of proinflammatory substances, such as cytokines, expressed at the surface of NP cells. In culture medium, these substances may be either inactivated or present in small amounts, explaining the absence of effects on NCV.

All the above-mentioned studies were conducted using normal NP. In humans with disk-related sciatica, however, the NP is altered by degenerative changes [77]. In addition, epidural application of anulus fibrosus in the same model has received little attention. In one study, anulus fibrosus had no effect on NCV, and NP affected with degenerative disease exerted similar electrophysiological effects to those produced by normal NP [78].

3.4. Recapitulation of experimental data on the effects and nature of chemical factors

NP has been shown to induce axonal and myelin sheath alterations [39,68,69,75,79], increase vascular permeability [47,80], cause intravascular coagulation [47], and diminish intraneural blood flow [81]. These effects were variably inhibited by methylprednisolone [69,70], diclofenac [71], indomethacin [74], and cyclosporine (unpublished data). They were probably generated by NP cells [75] and more specifically by substances or structures located at the cell surface [76].

The proinflammatory effects of NP demonstrated in these studies resemble those seen with TNF-α, which therefore emerges as a likely culprit in the genesis of disk-related sciatica [82–84]. TNF-α can induce nerve lesions [85,86] including myelin alterations similar to those seen after exposure to NP [86–90]. TNF-α increases vascular permeability [86,87] and triggers coagulation events [91]. In addition, TNF-α can be inhibited by corticosteroids [92,93] and cyclosporine [93,94]; weaker inhibition is seen with nonsteroidal antiinflammatory agents [95,96].

Animal studies have established that NP exposure can cause pain-related behavioral changes including pain hypersensitivity [68]. TNF-α has produced similar effects, as well as documented neuropathy [84,86,89,97,98]. To confirm the TNF-α hypothesis, a study was conducted in the pig model developed by Olmarker and Larsson [101]. TNF-α was identified in NP cells, although its exact location (cytosol, cell surface, or both) was not determined. The potent TNF-α inhibitor doxycycline [99,100] completely abolished the NVC decrease usually produced by NP; thus, the findings were similar to those reported with retroperitoneal fat (control) in other studies. Monoclonal antibodies to pig TNF-α decreased but did not abolish the NCV reduction, although the authors suggested that abolition would perhaps have been achieved with larger anti-TNF-α dosages [101].

The finding that doxycycline inhibits the effects of NP deserves careful analysis, as this compound blocks not only TNF-α, but also IL-1 [102], interferon-γ [99], NO synthetase [103], and several metalloproteases [100,102]. IL-1, interferon-γ, and other substances act synergistically with TNF-α and can induce neurotoxicity [98,104–106]; in addition, they are inhibited by corticosteroids and cyclosporine [92]. Thus, IL-1, interferon-γ, NO synthetase, and other substances may contribute, together with TNF-α, to generate the effects of NP in Olmarker’s pig model. Nevertheless, data are more abundant for TNF-α, warranting the use of TNF-α antagonists for the first clinical trials [107].

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Fat*</th>
<th>Killed fibroblasts</th>
<th>Live fibroblasts</th>
<th>Culture medium</th>
<th>Killed NP cells</th>
<th>Live NP cells</th>
<th>NP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCV (m/s)</td>
<td>76 ± 11</td>
<td>72 ± 8</td>
<td>63 ± 10</td>
<td>66 ± 9</td>
<td>52 ± 10*</td>
<td>50 ± 10*</td>
<td>45 ± 19*</td>
</tr>
</tbody>
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| *P < 0.05 comparatively to the fat, fibroblasts, and culture medium groups.  
* Results from a previous experiment [56].

3.5. Reciprocal role of cytokines and chemical factors

References


