The Inflammatory Properties of the Intervertebral Disc

As we travel through the US and teach, it amazes us as a faculty, how few therapists are aware of the inflammatory issues of the intervertebral disc, and how it relates to a movement profession such as physical therapy. The first we heard of this information was through a great pioneer, Dr. Lance Twomey. Dr. Twomey showed us, through meticulous dissections that the conventional model of a disc bulging out against a nerve root is not only very unlikely, but that mechanical compression of a nerve only produces paresthesia and numbness. Discs do bulge, but is usually contained within/around the posterior longitudinal ligament. Furthermore a mechanical model that teaches a disc pushes against a nerve root, facilitates interventions such as surgery, and questions how therapy would be beneficial. The inflammatory properties-of-the-disc model have been introduced and taught for over 20 years. Here’s a brief summary:

- The primary changes to the disc are preempted by selective bone loss to the vertebral body, causing the cartilage endplate to bend and undergo stress.

- With loading and trauma, the cartilage endplate fractures and a protein in the nucleus (proteoglycan) suck fluid into the disc. Since blood is housed in the vertebrae, the nucleus fills with blood. This usually takes 24 – 48h. If there are no previous tears (see below), the patient has a contained disc lesion – extremely painful, load sensitive and pain with coughing and sneezing.

- If, however a patient has had several episodes of back pain in their life, the disc would have had numerous tears (fissures) thus weakening the disc. Once blood enters the nucleus as above, it mixes with the proinflammatory chemicals (phospholipase A2 (PLA2) and thorough the fissure the blood and inflammatory chemicals exists the disc and create a chemical irritation of the nerve root, resulting in pain. If the bleeding is excessive, swelling and thus a mechanical pressure is also exerted, which causing pins and needles and numbness along with the pain.

- This inflammatory model is the model taught by and followed by anesthesiologists, pain management and interventional radiologists, whom inject steroids into the affected area, thus decreasing the inflammation and reducing the swelling.

- Why so adamant about this? Therapy, a movement-based profession has a lot to offer such a patient. Fluid transfer in/around the disc is dependent on movement. Extension exercises facilitate fluid in/around the disc and nutrition of the disc, but also around the proximal nerve root – most likely the reason for “centralization.” Oscillatory techniques such as spinal mobilization could be argued, enhance blood flow around the foramen. Neural tissue mobilization helps with movement in/around the foramen. Spinal manipulation cavitations may change pressure around the nerve root. Spinal positioning can help create space and decrease pressure in the disc (Nachemson). Gentle exercise will help stimulate blood flow in/around the foramen.

THE RESEARCH Three pioneer articles that may be of benefit:

The inflammatory effect of the nucleus pulposus: A possible element in the pathogenesis of LBP
McCarron et al Spine 1987; Volume 12; Number 8; pages 760 - 764

Internal disc disruption: A challenge to disc prolapse fifty years on
Dr. HV Crock Spine 1986; Volume 11; Number 6; 1986: page 650 – 653

The role of inflammation in lumbar pain
Joel Saal, MD Spine 1995; Volume 20; Number 16; pages 1821 – 1827
**Phospholipase A2 Activity in Herniated Lumbar Discs: Clinical Correlations and Inhibition by Piroxicam.**  

Several studies suggest disc inflammation as a mechanism of sciatica due to disc herniation, and phospholipase A2 emerges as a key enzyme of cartilage and disc tissues.

**Methods:** Phospholipase A2 activity was determined, using the degradation of a specific substrate, in the serum and discs of 31 patients (14 treated with acetaminophen and 17 treated with piroxicam) undergoing surgery for sciatica due to lumbar disc herniation. Visual analog scale for pain, Dallas Pain Questionnaire, Lasegue’s sign, radiographic stage of degeneration of the herniated disc, volume of disc herniation shown by computed tomography, and surgical findings were recorded.

**Results:** Disc phospholipase A2 activity was independent of the patient’s age or sex, the radiologic stage of disc degeneration, and the volume of the herniation, and showed no significant correlation with Lasegue’s sign or pain measured on a visual analog scale. The correlation between disc phospholipase A2 and the Dallas category of items measuring the impact of pain on daily activities approached the level of significance (P = 0.07). Disc phospholipase A2 activity was significantly higher in cases of sequestrated discs than in other herniations. Disc phospholipase A2 was significantly correlated with serum phospholipase A2, and was significantly lower in patients treated with piroxicam than in those treated with acetaminophen.

**Conclusions:** Disc phospholipase A2 is thought to participate in the physiopathology of sciatica and to be modulated by nonsteroidal anti-inflammatory drug therapy. Serum phospholipase A2 is suggested as a biologic marker of disc inflammation in patients with sciatica.

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**A Controlled Biochemical and Immunohistochemical Study of Human Synovial-Type (Group II) Phospholipase A2 and Inflammatory Cells in Macroscopically Normal, Degenerated, and Herniated Human Lumbar Disc Tissues.**  

**Summary of Background Data:** It has been suggested that a high phospholipase A2 enzyme activity in herniated disc tissue could be significant in abnormal states such as sciatica and discogenic pain. No comparison between healthy disc tissue and samples of abnormal discs (degenerated or herniated) has been carried out. In particular, an identical assay for phospholipase A2 for such tissue samples, supported by immunohistochemical staining data, has never been applied in parallel to normal and abnormal disc tissue, and neither have such results been compared with the demonstration of inflammatory cells.

**Methods:** Group II phospholipase A2 enzyme activity was determined, in parallel, using an identical assay for tissue samples from 11 macroscopically normal discs, 33 disc herniations, and six discs showing degeneration by discography. For determination of phospholipase A2 enzyme activity, a radioassay using 1-palmitoyl-2-(1-14C)linoleoyl-L-3-phosphatidylethanolamine as the phospholipid substrate was used. Total tissue DNA as an estimate of total tissue cell number was measured in parallel with phospholipase A2 activity. All tissue samples also were studied by indirect immunocytochemistry, locating phospholipase A2 and T and B lymphocytes.

**Results:** Neither degenerated nor herniated disc tissue samples demonstrated a higher phospholipase A2 activity than control disc tissue samples. Average phospholipase A2 activity was actually higher in the control samples than in herniated disc samples (Mann-Whitney test, P < 0.001), possibly a result of a higher total DNA (P < 0.005). The observed level of phospholipase A2 activity was lower than that of inflammatory human synovial fluid. Neither was there marked immunoreactivity for phospholipase A2, which was observed in chondrocytes in areas of cartilage and occasional disc cells, supporting the biochemical results. Lymphocytes were more numerous only in herniated disc samples (15%), and their presence showed little overlap with phospholipase A2 immunoreactivity.

**Conclusions:** Synovial-type (Group II) phospholipase A2 enzyme activity is not particularly high in disc tissue and does not appear to be higher in herniated or degenerated discs than control disc tissue. Immunoreactivity to phospholipase A2 is seen only occasionally and is strong only when cartilage tissue is present. Neither are inflammatory lymphocytes commonly observed.
Effects of Cyclic Mechanical Stress on the Production of Inflammatory Agents by Nucleus Pulposus and Anulus Fibrosus Derived Cells In Vitro.


It has been reported that CMS affects degeneration of the disc. However, little is known about the effect of CMS on the production of inflammatory agents by both cell types in vitro.

Methods: Cells derived from nucleus pulposus and anulus fibrosus of Sprague-Dawley rat tails were cultured with or without CMS applied by the Flexercell Strain Unit (Flexcell International Corp., Hillsborough, NC) in the presence or absence of inflammatory stimulus. Doses of prostaglandin-E2 (PGE2) were measured in the culture supernatants. Semiquantitative evaluations of the expressions of cyclooxygenase (COX)-2 and phospholipase-A2 IIA messenger ribonucleic acids (mRNAs) were also examined.

Results: Application of CMS on nucleus pulposus and anulus fibrosus cells increased PGE2 synthesis. Coincidence of CMS and inflammatory stimulus synergistically enhanced PGE2 synthesis of both cell types. Anulus fibrosus cells showed a stronger reactivity to these stimuli than nucleus pulposus cells. The expression of COX-2 mRNA of anulus fibrosus cells tended to correlate to the amount of PGE2, whereas COX-2 mRNA was constitutively expressed in nucleus pulposus cells, suggesting that the roles of COX-2 might be different between nucleus pulposus and anulus fibrosus. Phospholipase-A2 IIA mRNA was constitutively expressed in both cell types.

Conclusions: The results of this study suggested that CMS might be involved in the pathomechanism of pain induction of lumbar disc diseases.

Phospholipase A2 Sensitivity of the Dorsal Root and Dorsal Root Ganglion.


Phospholipase A2 may be an irritating component of disc tissue that is present in high concentration in painful herniated discs, in synovial fluids, and in sera of rheumatoid arthritis patients. Phospholipase A2 is inflammatory; however, its effects on dorsal roots and dorsal root ganglion response have never been demonstrated.

Methods: Surgically isolated dorsal roots and dorsal root ganglia from New Zealand White rabbits were investigated by electrophysiologic techniques. Phospholipase A2 doses ranging from 100 to 400 U were applied on the mechanically sensitive segments of the dorsal root ganglia, and responses to varying doses were evaluated in relation to elapsed time.

Results: The application of phospholipase A2 on the dorsal root ganglion resulted in possible neurotoxicity at doses more than 375 U, with no significant effect at lower doses except for recruitment of “silent units” at doses ranging from 200 to 340 U.

Conclusions: Phospholipase A2 doses comparable to serum concentrations in human rheumatoid arthritis appeared to be neurotoxic when applied to dorsal root ganglia. At lower doses, silent units become activated that were not active before the phospholipase A2 application. These results suggest that dorsal roots and dorsal root ganglion may be impaired by phospholipase A2, leading to sciatica and low back pain.

The Role of Steroids and Their Effects on Phospholipase A2: An Animal Model of Radiculopathy.


There have been several reported animal models of peripheral neuropathy. Recently an animal model that shows reliable behavioral and neurochemical changes was proposed, and epidural steroid injections in this model were effective in the reduction of thermal hyperalgesia and allodynia.

Method: In a behavioral study, 24 rats were divided into 4 groups: Group I, loose ligature of the left L4 and L5 nerve roots with 4-0 chromic gut sutures and an epidural injection of 0.1 mL of saline at 3 days after surgery; Group II, same as Group I but with an epidural injection of 0.1 mL of betamethasone on the day before the operation; Group III, same as Group II except injection at 1 day after surgery; Group IV, same as Group II except injection at 3 days after surgery. To test the phospholipase A2 activity in the nerve roots and dorsal root ganglia after the operation, eight rats were killed at given intervals. Analysis of variance techniques were used to test behavioral pattern changes and phospholipase A2 activity across time in each group.

Results: Thermal hyperalgesia reached its maximal point at 3 weeks after surgery in Group I, but in steroid injection groups, the recovery from hyperalgesia was faster than in Group I. However, there was no significant difference in recovery time among steroid injection groups. The level of phospholipase A2 activity was at its maximum at 1 week after surgery in Groups I and IV. It showed a steady reduction in the steroid group, whereas it remained relatively high and dropped rapidly after 3 weeks in the saline treated group, and returned to the level of a normal nerve root at 6 weeks after surgery.

Conclusion: These results suggest that the behavioral pattern changes observed in the irritated nerve root model are caused in part by a high level of phospholipase A2 activity initiated by inflammation, and that the mechanism of action of epidural steroid injection in this model is inhibition of phospholipase A2 activity.

The pathophysiology of sciatica is uncertain, although mechanical, chemical, and ischemic factors have been proposed.

Methods: Phospholipase A2 was injected into the rat L4-L5 epidural space, and the rats were observed for 3 or 21 days. Behavioral studies were conducted daily during the survival period. On the 3rd or 21st day, extracellular nerve recordings were made from dorsal roots, to determine discharge properties and mechanical sensitivity. The nerve roots were then sectioned for a light-microscopic examination.

Results: Motor weakness of hind limbs and altered sensation were observed. In the 3-day phospholipase A2 groups, squeezing the dorsal roots at the L4-L5 disc level (force = 0.8 g) evoked sustained ectopic discharge that lasted approximately 8 minutes. Squeezing the roots distal to the L4-L5 area did not result in sustained discharges. In sham, control, and 21-day phospholipase A2 groups, squeezing the dorsal roots elicited only a transient firing that lasted approximately 0.1 second. Loss of myelin was seen in the nerve root cross sections in the 3-day group, and remyelination was observed in the 21-day group. No abnormality was found in the control groups.

Conclusions: Based on these studies, it is hypothesized that phospholipase A2 causes demyelination that results in hypersensitive regions where ectopic discharge may be elicited by mechanical stimulation. These ectopic discharges may be a source of sciatica. We believe that, as long as these irritating factors are present, the hypersensitive nerve root nerve will continue to fire, and sciatic pain will persist.

Prostaglandin Production After Experimental Discectomy.
Spine. 21(15):1731-1736, August 1, 1996.

Previous studies have shown that nuclear material obtained from degenerative discs manifests an extraordinarily high level of phospholipase A2 activity. Others have hypothesized that the known inflammatory effects of phospholipase A2 are due to the release of arachidonic acid, which is converted to various eicosanoids, including several algesic prostaglandins (PGI2 and PGE2). No previous study has continuously measured prostaglandin levels in epidural fluid or assessed the effect of discectomy on prostaglandin production.

Methods: An ultrafiltrate of lumbar epidural fluid of dogs was obtained from indwelling catheters located adjacent to spinal areas that were and were not subjected to discectomy as well as from subcutaneous tissue. The fluid was collected daily for 14 days and analyzed for PGE2 and 6-keto PGF1[alpha] (the stable metabolite of PGI2) by radioimmunoassay.

Results: The concentration of 6-keto PGF1[alpha] and PGE2 in fluid collected during the first 24 hours was significantly higher in the area of discectomy than in the epidural region that was not subjected to discectomy and significantly higher than in fluid obtained from the subcutaneous site. The high level of these prostaglandins at the discectomy site fell rapidly, so that by the end of 48 hours the differences in values between spinal fluid from the discectomy and nondiscectomy regions were not statistically significant. The concentration of the prostaglandins in epidural fluid decreased with time and became minimal within the second week.

Conclusion: The removal of normal discs is accompanied for 24 hours by a marked rise in the synthesis of two prostaglandins known to produce pain. Because the concentration of prostaglandins in epidural fluid decreased rapidly thereafter, the initial surge obtained appears to be associated more with chemical factors such as phospholipase A2 than with wound healing.

The Effect of Epidural Injection of Betamethasone or Bupivacaine in a Rat Model of Lumbar Radiculopathy.

Epidural injections are commonly used for the treatment of low back pain and sciatica. However, efficacy remains controversial, and there is a paucity of basic information to support clinical use or the injections.

Methods: Fifty-one rats were used. The left L4 and L5 nerve roots were loosely ligated with chromic gut, and either betamethasone, bupivacaine, betamethasone in combination with bupivacaine, or saline was injected using an epidurally placed catheter. The effects of epidural injection were evaluated using response to noxious stimuli and immunohistochemical methods.

Results: In betamethasone-treated rats (either alone or in combination with bupivacaine), thermal hyperalgesia was significantly less (P < 0.01) after surgery than that in saline- or bupivacaine-treated groups, in which the hyperalgesia was maximum at 2-3 postoperative weeks before resolving 5 weeks after surgery. Immunohistochemical analysis did not correlate with these results.

Conclusions: Epidural steroid injection has a significant effect on the thermal hyperalgesia produced in a model of radiculopathy, which may provide clinical support for advocates of epidural steroids.
The Inflammatory Properties of Contained and Noncontained Lumbar Disc Herniation.  

High levels of phospholipase A2 previously have been demonstrated in a small number of patients undergoing lumbar disc surgery. Phospholipase A2 is the enzyme responsible for the liberation of arachidonic acid from cell membranes at the site of inflammation and is considered to be the limiting agent in the production of prostaglandins and leukotrienes, which are powerful mediators of inflammation. Cytokines are among the many agonists inducing phospholipase A2 activation. Several reports previously have demonstrated the difference in clinical appearance of different types of lumbar disc herniation.

Methods: Thirty-seven patients undergoing surgery for lumbar disc herniation were investigated. During surgery the disc pathology of each patient was classified into one of three groups: bulging disc, contained herniation, and noncontained disc herniation. Also during surgery, biopsy samples were taken from the nucleus, immediately frozen in liquid nitrogen, and subsequently stored at -70 C until analyzed.

Results: No traces of interleukin-6 or tumor necrosis factor alpha were found in the biopsy samples. There was a significant difference in the levels of leukotriene B4 and thromboxane B2 in contained versus noncontained disc herniation, and the highest concentration was found in the noncontained disc herniation group.

Conclusion: The results support the theory that inflammatory mechanisms are involved in sciatica because of lumbar disc herniation and indicate that the different types of disc herniation have different inflammatory properties.

The Efficacy of Corticosteroids in Periradicular Infiltration for Chronic Radicular Pain: A Randomized, Double-Blind, Controlled Trial.  

Various studies have examined the therapeutic value of periradicular infiltration using treatment agents consisting of local anesthetic and corticosteroids for radicular pain, secondary to lumbar disc herniation and spinal stenosis. There is currently no randomized trial to determine the efficacy of a single injection of corticosteroids for chronic radicular pain.

Methods: Eligible patients with radicular pain who had unilateral symptoms who failed conservative management were randomized for a single injection with bupivacaine and methylprednisolone or bupivacaine only. Outcome measures included the Oswestry Disability Index, visual analogue score for back pain and leg pain, claudication walking distance, and the patient’s subjective level of satisfaction of the outcome.

Results: We recruited 43 patients in the bupivacaine and methylprednisolone group and 43 patients in the bupivacaine only group. The follow-up rate is 100%. Five patients had early termination of the trial for discectomy and further root block. There is no statistically significant difference in the outcome measures between the groups at 3 months (change of the Oswestry Disability Index [P = 0.68], change in visual analogue score [back pain, P = 0.68; leg pain, P = 0.94], change in walking distance [P = 0.7]). Duration of symptoms has a statistically significant negative association with the change in Oswestry Disability Index (P = 0.03).

Conclusion: Clinical improvement occurred in both groups of patients. Corticosteroids did not provide additional benefit.

Human Nucleus Pulposis Can Respond to a Pro-inflammatory Stimulus.  

Degenerate human disc tissue has been shown to spontaneously secrete a number of pro-inflammatory mediators. The importance of these molecules in the pathophysiology of symptomatic disc degeneration is increasingly recognized. Human nucleus pulposus has been shown to synthesize increased amounts of interleukin (IL)-6, prostaglandin E2 (PGE2), and nitric oxide in response to stimulation with IL-1[beta]. Murine nucleus pulposus synthesizes increased amounts of IL-1[beta], IL-6, IL-10, and granulocytemacrophage colony-stimulating factor in response to lipopolysaccharide stimulation. Lipopolysaccharide is a potent inducer of tumor necrosis factor-[alpha] (TNF-[alpha]), which is thought to play an important role in the pathophysiology of sciatica. To date, human nucleus pulposus has not been shown to secrete TNF-[alpha] in response to a pro-inflammatory stimulus.

Methods: Human disc tissue obtained from patients undergoing surgery for scoliosis, lumbar radiculopathy, and discogenic pain was cultured under basal and lipopolysaccharide-stimulated conditions and the medium subsequently analyzed for a range of pro-inflammatory mediators.

Results: None of the specimens produced any TNF-[alpha], IL-1[beta], granulocytemacrophage colony-stimulating factor,
or leukotriene B4. Measurable quantities of IL-6, IL-8, PGE2, MCP-1, basic fibroblast growth factor, and transforming growth factor-[beta]1 were produced by a number of specimens. Lipopolysaccharide significantly increased IL-6, IL-8, and PGE2 production in both control and degenerate disc tissue. Degenerate disc specimens responded more vigorously to lipopolysaccharide stimulation than scoliotic specimens.

Conclusions: We conclude that both scoliotic and degenerate human nucleus pulposus can respond to an exogenous pro-inflammatory stimulus by secreting increased amounts of IL-6, IL-8, and PGE2 but not TNF-[alpha] and that degenerate disc tissue is more sensitive to a pro-inflammatory stimulus than its scoliotic counterpart.

The Role of Cyclooxygenase-2 in Lumbar Disc Herniation.
Spine. 27(22):2477-2483, November 15, 2002.

Prostaglandin E2 is one of the most important mediators contributing to pathogenetic components of lumbar disc herniation. Cyclooxygenase-2, the rate-limiting enzyme of prostaglandin E2 synthesis, has been identified and extensively investigated in other inflammatory diseases. However, the role of cyclooxygenase-2 in lumbar disc herniation has never been addressed.

Methods: Fifteen specimens from patients with lumbar disc herniation and five control discs from traumatic burst fracture were harvested. The expression of cyclooxygenase-2 was evaluated immunohistologically. The ability of cultured disc cells to produce prostaglandin E2 with inflammatory stimulus in the presence or absence of a selective inhibitor of cyclooxygenase-2 was investigated. At the same time, the induction of cyclooxygenase-2 mRNA of these cells by reverse transcriptase-polymerase chain reaction was detected. The manner in which this prostaglandin E2 production could be suppressed by various doses of a cyclooxygenase-2 inhibitor also was investigated.

Results: Immunohistologically, the expression of cyclooxygenase-2 was observed only in the lumbar disc herniation specimens. The cultured cells had a strong ability to produce prostaglandin E2 coinciding with cyclooxygenase-2 mRNA induction. A selective inhibitor of cyclooxygenase-2 inhibited this prostaglandin E2 production in a dose-dependent manner.

Conclusion: Cyclooxygenase-2 might be involved in the pathogenesis of lumbar disc herniation through upregulation of prostaglandin E2 production.

Effect of Nucleus Pulposus on the Neural Activity of Dorsal Root Ganglion.

It has been suggested that the epidural application of autologous nucleus pulposus without mechanical compression causes nerve root inflammation and related radicular pain in lumbar disc herniation. Concerning the dorsal root ganglion, its mechanical hypersensitivity and potential for generating ectopic discharges have been reported. However, the effect of autologous nucleus pulposus on the dorsal root ganglion is uncertain.

Methods: In adult Sprague-Dawley rats spontaneous neural activity was recorded from the surgically exposed L5 dorsal root using electrophysiologic techniques, and the mechanosensitivity of L5 dorsal root ganglia and corresponding receptive fields on the hind paw were measured using calibrated nylon filaments. Autologous nucleus pulposus from the tail or fat was implanted at the L5 nerve root. Neural activity was monitored for 6 hours.

Results: Spontaneous neural activity in the nucleus pulposus group gradually increased and showed significant differences compared with the fat group from 2.5 to 6 hours after exposure. The mechanosensitivity of the dorsal root ganglia showed significant increases compared with the fat group.

Conclusions: After application of nucleus pulposus to the nerve root, the dorsal root ganglion demonstrated increased excitability and mechanical hypersensitivity. These results suggest that nucleus pulposus causes excitatory changes in the dorsal root ganglion.