Effects of Nucleus Pulposus on Nerve Root Neural Activity, Mechanosensitivity, Axonal Morphology, and Sodium Channel Expression

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Study Design. This study analyzed the effects of autografted nucleus pulposus on nerve root axon morphology, neurophysiologic function, and sodium channel expression.

Objectives. To investigate the chronic effects of the epidural implantation of nucleus pulposus on nerve root morphology, neural activity, ectopic discharge, mechanosensitivity, and sodium channel expression.

Summary of Background Data. It has been reported that ectopic discharges were recorded antidromically from sural nerve on compressing nucleus pulposus exposed spinal nerves. However, it is not clear what the effects of nucleus pulposus are on ectopic discharges recorded directly from the spinal nerve roots. It is also not clear what the effects of nucleus pulposus are on the threshold pressure to provoke ectopic discharges in the spinal nerves. Sodium channel content increases in remodeling axons after nerve injury, but it is not clear what the effects of nucleus pulposus are on sodium channel expression in spinal nerve.

Methods. Forty-six male Sprague-Dawley rats were used, 20 in a nucleus pulposus-implanted group, 18 in a fat-implanted group, and 8 in a normal group. Fresh autografted nucleus pulposus or fat tissue was implanted into the dorsal epidural space at the L4–L5 disc level. On the 7th, 21st, or 42nd day, neurophysiologic recordings were made to determine nerve root response to compression. Nerve roots were then harvested to determine sodium channel protein concentration and histologic changes in the nerve root. The correlations between sodium channel density and neural activity and mechanosensitivity of dorsal root were analyzed statistically.

Results. Ectopic discharge rate was higher in nucleus pulposus 7-day group. Threshold pressure to evoke ectopic discharges was lower in the nucleus pulposus 7-day group, and higher in the nucleus pulposus 42-day group compared to the normal group. Sodium channel protein density increased in the nucleus pulposus 7-day and nucleus pulposus 21-day group compared to normal nerve.

Sodium channel density changes were not correlated to threshold pressure. Ectopic discharge rate increased with increase of sodium channel density in the nerve roots. The number of axons with neuropathy increased in the nucleus pulposus 7-day and 21-day groups.

Conclusions. Acute exposure of nerve root to nucleus pulposus resulted in increased number of axons with neuropathy, higher intensity of ectopic discharges on compression, and nerve mechanosensitization. Chronic exposure resulted in mechanical desensitization. Changes of sodium channel density were correlated to ectopic discharge rate. [Key words: nucleus pulposus, nerve root, neurophysiology, mechanosensitivity, sodium channel protein, axonal histology, Schmidt-Lanteman incisure] Spine 2004;29:17–25

The mechanisms for sciatic pain and paresthesia caused by lumbar disc herniation are still not completely clear. That compression on the spinal nerve can cause clinical symptoms is accepted widely. However, it has been reported that mechanical compression of spinal nerve roots can cause impairment without associated pain or is not associated with pain in all circumstances. Rupture of disc with sequestration of nucleus pulposus (NP) into the epidural space usually causes severe sciatic pain. Removal of NP by chemonucleolysis relieves sciatic pain even though compression of nerve root is still shown in computer-assisted tomographic scan. These data suggest that effects of NP on the spinal nerve may play an important role in generation of sciatic pain.

Several neurophysiologic studies have been performed to investigate the effects of NP on conduction velocity of axons. However, it is not clear if epidural NP affects spontaneous activity in the axons of the spinal nerve. Paresthesia and numbness are generated due to change of spontaneous activity. Decrease of spontaneous activity in the spinal nerve may indicate loss of nerve conduction in the pathway.

The nerve roots under epidural or local anesthesia have been shown to be very sensitive to compression; uncomfortable sensation and sciatic pain can be produced in response to mechanical manipulation on the nerve root in patients with herniated NP. Compression on nerve roots with chronic constriction can produce ectopic discharges including nociceptive activity. Threshold pressure for ectopic discharges can be changed after exposure of nerve root to phospholipase A2. However, it is not clear that exposure of nerve
roots to NP can result in changes of threshold pressure required to evoke ectopic discharges.

Sodium channels play an important role in the neural activity including action potential generation and conduction. Considerable attention has been focused on the role of sodium channels in the pathophysiology of neuropathic pain and as therapeutic targets. Increased expression of sodium channel occurs at the neuroma forming sites where nerve is injured. However, it is not clear if exposure of nerve root to NP leads to abnormal sodium channel expression including accumulation and redistribution.

Exposure of nerve root to NP for 7 days causes vacuolar swelling of the Schmidt-Lanterman incisures. It is not clear what the chronic effects of NP are on the axon morphology that accounts for functional changes of the spinal nerve after more than 7-day exposure. It is necessary to observe histologic changes in the nerve root so as to better understand axonal functional changes.

Our hypotheses are that NP affects spontaneous neural activity, intensity of ectopic discharges, threshold pressure to provoke ectopic discharges, and sodium channel protein expression in the axons. The purpose of this study was to better understand the neurophysiologic changes caused by herniated NP and related histologic and molecular biologic changes.

### Materials and Methods

#### Preparation of the Animals

Forty-six male Sprague-Dawley rats weighing 350 to 450 g were used in this double-blind study. Twenty were in an NP-implanted group surviving for 7, 21, or 42 days (n = 7, 7, and 6, respectively). Eighteen were in a fat-implanted group surviving for 7, 21, or 42 days (n = 6, 6, and 6, respectively), and 8 were in a normal group (rats without previous surgery) (Table 1). In surgery for the implantation of NP, sodium pentobarbital (initial dose of 25–40 mg/kg, maintenance dose of 8–10 mg/kg intraperitoneal) was used to anesthetize the rats. This study was approved by the Institutional Animal Investigation Committee.

Nucleus pulposus harvested from coccygeal disks was placed into the lumbar epidural space of the same rat. A dorsal tail incision was made to remove coccygeal 3, 4, and 5 spinal processes and lamina to expose the coccygeal intervertebral disks 3–4 and 4–5. After a hole was made in the anulus fibrosis, a small tip curette was used to extract NP (approximately $1.5 \times 1.0 \times 1.0 \text{ mm}^3$ in total volume). A midline lumbar incision was made to expose the left ligamentum flavum between L4 and L5 lamina. Under a surgical microscope, a longitudinal incision was made on the left ligamentum flavum. Dumont microsurgical forceps were used to pull the ligamentum flavum open to expose the epidural space. The NP or fat was implanted into the L4–L5 epidural space centrally (Figure 1). The ligamentum flavum was released back to the previous position, and NP or fat was closed in the spinal canal by the ligamentum flavum. The wound of the ligamentum flavum was not sutured. This wound closed by itself due to tension on ligamentum flavum and implanted NP or fat sealed the incision. The wounds in the muscle and skin were closed using 4–0 silk suture. In the fat group, autografted subcutaneous fat tissue of the same volume as NP was implanted into the epidural space. Rats were monitored for 24 hours after the initial surgery for signs of distress. Buprenorphine (0.05 mg/kg, intramuscular, as necessary) was used to manage pain. Rats survived for 7, 21, or 42 days. All procedures were performed under sterile conditions.

#### Neurophysiologic Assessment

Extracellular nerve recordings were made from fat, normal, and NP-exposed dorsal roots on the 7th, 21st, or 42nd day to determine neural activity and the response of dorsal roots to mechanical probing. The anesthetized rat was clamped at two spinous processes (L2 and S1) using a spine-holding device. A laminectomy was performed from L3 to L6 to expose the nerve roots. The exposed nerves and surrounding tissue were immersed in a pool of mineral oil heated to 37 C. A pair of platinum bipolar hook recording electrodes were placed on the proximal L5 nerve root segment to record neural activity. The intent of this study was to monitor neural activity and examine sodium channel expression in response to NP by recording extracellular nerve activity.

![Figure 1](image.png)

**Figure 1.** The nucleus pulposus or fat was implanted into the L4–L5 dorsal epidural space close to the spinous process. Nucleus pulposus or fat sealed the wound in the ligamentum flavum below the incision.
itor response of whole dorsal roots rather than split nerve root – ing. The nerve segment of L5 dorsal root passing over L4
Figure 2. Schematic diagram of setting for neural activity record-
recorder, and recorded on an FM tape recorder (MR-30; 
er, displayed on an oscilloscope, monitored through an audio
nerve activity was recorded from dorsal roots without
Mechanosensitivity was determined by measuring the min-
meric compression were then recorded. Neural activity provoked
The pressure provoking ectopic discharges was regarded as
The analog tape data were then digitized and analyzed on a
Measurement of Sodium Channel Protein Density in the
Dorsal Root. After neurophysiology recordings, the left L5,
immunofluorescence studies for sodium channels. The right L5,
Immunochemical Staining Studies for Sodium Channels.

Effects of NP on Nerve Root • Chen et al 19

Figure 2. Schematic diagram of setting for neural activity record-
ing. The nerve segment of L5 dorsal root passing over L4–L5 disc
level was placed on a supporting platform and probed with nylon
filaments attached to a load cell transducer. A pair of platinum
bipolar hook recording electrodes was placed at the proximal
segment to record neural activity.

Nerve activity from the L5 dorsal root was recorded in sev-
Several stages. Spontaneous neural activity was recorded first. This
nerve activity recorded from dorsal roots without stimulat-
ing the peripheral tissue or dorsal root and was defined as
baseline discharge. The responses of nerve root to me-
canical compression were then recorded. Neural activity provoked
from compressing the L5 dorsal root was regarded as ectopic
discharges.

The intensity of neural activity was determined by the total
number of action potentials per second, termed discharge rate.
The ectopic discharge rate equaled total discharge rate re-
corded on probing the nerve minus the baseline discharge rate.
Mechanosensitivity was determined by measuring the min-
imum pressure (threshold pressure) that could provoke abnor-
mal neural activity. The L5 nerve root at the L4–L5 disc level
was probed using a calibrated nylon filament attached to a 10-g
load cell transducer. The signals from the load cell transducer
were amplified and sent through an analog-to-digital converter
to a computer and recorded together with neural activity. The
tip of the nylon filament was broadened into a flat and smooth
surface with an area of 1 mm². Force was applied by pressing
the nylon filament perpendicularly against the nerve root that
rested on a plastic platform (Figure 2). A surgical microscope
was used to ensure the tip of nylon filament was applied at the
middle of the nerve root perpendicularly. The maximum force
applied did not exceed 10 g. The applied loading rate was 1.2 ±
0.6 g per second. The nerve segment between platform and
recording electrodes was draped loosely to avoid motion arti-
fact at the recording electrodes. The force was released when
ectopic discharges were provoked. Pressure applied was calcu-
lated by dividing the force in grams by the area of the tip of
nylon filament.

The pressure provoking ectopic discharges was regarded as
the threshold pressure to evoke ectopic discharges. The force
during probing time was shown on a personal computer screen
as a gradually increased force trace. Thus, at the moment when
ectopic discharges were provoked, the magnitude of force and
the probing time were determined precisely.

The analog tape data were then digitized and analyzed on a
computer using Enhanced Graphics Acquisition and Analysis
(EGAA) system (R.C. Electronics Inc., Goleta, CA). Using this
system, multunit discharge rate was determined by setting a
voltage threshold above which all spikes of nerve discharges
were counted. Each bar in the histogram showed the number of
discharges per second (impulse/s).

The nerves then were postfixed in 3% glutaraldehyde, buffer
rinsed overnight (4°C), osmicated (1% OsO₄, 4°C), dehy-
drated in ascending alcohols (4°C) and then in propylene oxide (20°C), and embedded in epoxy resin (Epon 812). Semithin sections (1 μm thick) were prepared for a light-microscopic examination. The sections were examined under a light microscope at 40 to 1000 magnification (Leica DML, Leica Microsystem Inc., Wetzlar, Germany). Photomicrographs were taken using a digital camera system attachment (Diagnostic Instruments Inc., Sterling Heights, MI).

Statistical Analysis. The time effects of NP on neural activity and mechanosensitivity were analyzed by analysis of variance (one-way ANOVA) and t test using SPSS software (Statistics Package for Social Science, Version 9.0, SPSS Inc. Chicago, IL). Comparisons were made between different groups to determine if differences had statistical significance. Linear regression and correlation analysis was performed between sodium channel density and neural activity including baseline discharge rate, ectopic discharge rate, ectopic discharge duration, threshold pressure, and probing time. P values less than 0.05 were considered significant. The averages are given as the mean ± standard deviation (SD).

Results

Neurophysiologic Assessment

Baseline Spontaneous Activity. The baseline discharge remained stable in all L5 spinal nerves before the nerve root was stimulated mechanically. Baseline discharge rate appeared to decrease 7 days after NP exposure compared to normal nerve (t test, P < 0.05) but not to fat exposed nerve (t test, P > 0.05). Baseline discharge rate returned to normal 21 days after exposure to NP (ANOVA, post hoc LSD, P > 0.05) (Figure 3A, Table 1). There was no statistical difference in baseline discharge among fat groups (ANOVA, post hoc LSD, P > 0.05).

Ectopic Discharge Activity. In this study, abnormal ectopic discharges were always evoked by mechanical compression on the dorsal root (Figure 4A and C). The ectopic discharge rate was higher in NP 7-day group than fat 7-day group (t test, P < 0.01) and normal group (t test, P < 0.05) (Figure 3B). The ectopic discharge rate in NP 21-day group appeared to be higher than normal group but without statistical significance (t test, P = 0.07). There was no difference between the NP 21-day group and fat 21-day group or between the NP 42-day group and fat 42-day group (t test, P > 0.05).

Mechanosensitivity of the Nerve Root. Pressing the L5 nerve root at the L4–L5 disc level provoked a discharge lasting approximately 0.6 seconds to 42 seconds in different rats. The average duration was 12 ± 10 seconds. There was no statistical difference for ectopic discharge duration between groups (ANOVA, P > 0.05).

The probing time required to provoke ectopic discharges varied from 0.2 seconds to 2.1 seconds in different roots. Probing time was based on the time required to elicit an ectopic discharge. The average probing time for all the roots was 1.34 ± 0.9 seconds. There was no statistical difference for probing duration between groups (ANOVA, P > 0.05).

The pressure that evoked ectopic discharges ranged from 0.2 to 7.5 g/mm². The average was 2.1 ± 1.3 g/mm². Nerve roots responded to mechanical compression with a sudden increase in discharge rate at the threshold pressure (Figure 4A). The discharges were sustained and then slowly returned to baseline discharge rate as shown in the histogram (Figure 4C). After the whole spinal root was separated from the spinal cord and dorsal root ganglia, probing the nerve segment over L4–L5 disc still evoked prolonged ectopic discharges.

Effects of NP on threshold pressure: compared to normal nerve root, threshold pressure in NP exposed nerve root changed over the exposure periods (ANOVA, P < 0.01) (Figure 5). Compared to normal rats, pressure to evoke ectopic discharges was lower in NP 7-day rats (t test, P < 0.05) and higher in NP 42-day rats (t test, P < 0.05) (Figure 5). There was no statistical difference in the threshold pressure between NP 21-day and normal group.

Effects of fat on threshold pressure: compared to normal nerve roots, changes of threshold pressure in fat exposed groups had no statistical difference over the periods studied. (ANOVA, P > 0.05 and t test, P > 0.05).

Comparisons between NP and fat groups: the thresholds pressure was lower in NP 7-day than in fat 7-day groups (t test P < 0.05). There was no statistical difference in the threshold pressure between NP 21-day and
fat 21-day rats. The threshold pressure was higher in NP 42-day than fat 42-day rats ($t$ test, $P < 0.05$).

**Density of Na$^+$ Channel in Nerve Root**

Na$^+$ channel protein (Type II) was found in all groups. The molecular weight was approximately 210 KDa (Figure 6A). In NP groups, sodium channel density increased on the seventh day ($t$ test, $P < 0.05$) and 21st day ($t$ test, $P < 0.01$) compared to normal rats and appeared to return to the normal level on the 42nd day (ANOVA and $t$ test, $P > 0.05$). In NP 42-day group, average sodium channel density was close to the normal but with bigger density variations.

In fat groups, sodium channel density was higher on the 21st day compared to the normal group ($t$ test, $P < 0.05$). There was no statistical difference in 7-day and 42-day fat groups compared with the normal group.

Sodium channel density was higher in NP 7-day group than fat 7-day group ($t$ test, $P < 0.05$), and higher in the NP 21-day group than fat 21-day group ($t$ test, $P < 0.05$). There was no statistical difference between NP 42-day group and fat 42-day group ($t$ test, $P > 0.05$) (Figure 6B).

**Relationship Between Nerve Discharge and Sodium Channel Density**

There was a correlation between baseline spontaneous discharge rate and sodium channel protein density ($r = 0.717$, $P < 0.01$) (Figure 7). Baseline discharge rate increased with sodium channel density increase. There was also a correlation between ectopic discharge rate and sodium channel protein density ($r = 0.745$, $P < 0.01$) (Figure 8). Ectopic discharge rate increased with sodium channel density increase. There was no correlation between the threshold pressure and sodium channel protein density ($P > 0.05$). There was also no correlation between ectopic discharge duration and sodium channel density.

**Histologic and Immunostaining Studies**

In the NP 7-day group (Figure 9B), vesicular and vacuolar degeneration in myelin sheath (arrow) was found. The number of Schmidt-Lanterman incisures (SLI)$^{20}$ appearing as double-rings increased significantly compared to the normal group ($t$ test, $P < 0.01$). These SLIs were dilated and had vesicular degeneration in incisural cytoplasm (asterisks in Figure 9B). In the NP 21-day group...
(Figure 9C), the number of SLIs also increased compared to normal group (*t* test, *P* < 0.05). Vesicular degeneration of incisures was also found in dilated incisural cytoplasm and myelin sheath (asterisks). Detachment of the myelin sheath from axolemma (arrow) was found (Figure 9C). In the NP 42-day group (Figure 9D), the number of Schmidt-Lanterman incisures was not different from the normal group. Myelin sheaths appeared to be slack with infold of myelin sheath into axonal cytoplasm (asterisks in Figure 9D).

The number of SLIs was higher in the NP 7-day group than in the fat 7-day group (*t* test, *P* < 0.01) and higher in the NP 21-day than the fat 21-day group (*t* test, *P* < 0.05). There was no statistical difference between the NP 42-day and fat 42-day group.

There was no statistical difference between the normal and fat groups for degenerated axons (ANOVA, *P* > 0.05, post hoc LSD).

**Discussion**

Our experimental design focused on the effects of autografted NP on the lumbar dorsal roots that conduct peripheral sensation and pain. Unnecessary injuries to spinal canal including laminectomy were avoided in this study. An incision on the ligamentum flavum was the only injury to the spinal canal. Surgical incision on the ligamentum flavum was small and the implanted autogenous NP or fat tissue could seal incision on the ligamentum flavum. This would minimize contact of the epidural space with the muscular wound outside the spinal canal. The same volume of fat tissue was used in this study as control and implanted in the same manner as NP.

**Effects of Nucleus Pulposus on Spontaneous Neural Activity**

Our data showed that 7 days after exposure to NP, spontaneous discharges decreased. This decrease of spontaneous baseline discharge rate indicates that neural activity from peripheral proprioceptors may be blocked. This may result from degeneration of axons in the nerve root. Peripheral neural signals could be blocked at the degenerated segment so that these peripheral signals could not be recorded at the proximal nerve segment. Loss of neural activity propagated to the central nervous system may be the reason for numbness.

**Effects of Nucleus Pulposus on Intensity of Ectopic Discharges**

Ectopic discharge rate reflects the amount of neural activity provoked from the degenerated nerve segment. Our data showed that ectopic discharge rate was higher in the NP 7-day group (*P* < 0.05) and had a tendency to be higher in the NP 21-day group (*P* = 0.07). Higher ectopic discharge rate may manifest as more intense pain and paresthesia as reflected by more severe symptoms clinically during the acute stage of disc herniation.

**Nucleus Pulposus-Induced Mechanosensitivity Changes**

In this study, pressing the nerve root segment always elicited ectopic discharges that were recorded from the proximal segment of the spinal nerve. However, the pressure required to evoke ectopic discharges was different in different groups. The pressure to evoke discharges was lower in NP exposed nerve roots on the 7th day and higher on the 42nd day compared to normal nerve roots and compared with fat exposed nerve roots.

Change of mechanosensitivity may be due to changes of axonal mechanical properties. Neuropathic myelin sheaths and SLIs may cause axonal mechanical property changes that make axons vulnerable to compression. Micromechanical trauma to the axons can result in influx of calcium ion into the cell via a leakage pathway. Influx of cations can change intracellular voltage resulting in sodium channel activation and ectopic discharges. The pressure to evoke ectopic discharges was higher in the 42-day NP exposed nerve roots, meaning they were less sensitive to mechanical probing. This desensitization
may be due to decreased tension on the axonal membrane as myelin sheath appeared slack in our histologic data.

**Mechanosensitivity Changes Were Not Related to Na\(^+\) Channel Density**

We hypothesized that changes of sodium channel density would lower the mechanical threshold to evoke ectopic discharges. However, the results showed that there was no correlation between sodium channel density and threshold pressure. These data indicated that change of sodium channel density might not contribute to the change of threshold pressure. Sodium channels are voltage-gated and compression on axons should not open sodium channels.

**Nucleus Pulposus-Induced Change of Sodium Channel Density**

In this study, sodium channel density increased in the NP 7-day and 21-day exposed nerve roots using a Western Blot method. This indicates that NP affects sodium channel protein biosynthesis in the involved axons that might induce sodium channel redistribution and accumulation.

Using an immunostaining method to stain sodium channels, the myelin of axons appeared to be stained darker in NP groups than in normal and fat groups under light microscopy. However, further studies using electron microscopy are required to locate immunostained sodium ion channels in the axonal membrane and to perform quantitative studies.

**Effects of Nucleus Pulposus on Axonal Structures**

Our data showed that application of NP in epidural space induced neuropathic changes in myelin sheaths and SLIs\(^{15,22,23}\) (Figure 9B through 9D). The number of SLIs with pathologic changes increased in 7 days' and 21 days' NP exposed nerve roots. These pathologic changes included vesicular and vacuolar degeneration in myelin sheath,\(^{24}\) dilation and vesicular degeneration in incisural cytoplasm,\(^{15,24}\) and detachment of myelin sheath.\(^{25}\) Less neuropathic SLIs were found in 42 days' NP exposed nerve roots, but myelin sheath appeared slack with infolds of myelin sheath into the axonal cytoplasm.\(^{20,25,26}\) This indicates that neuropathic changes in axons may gradually recover after being exposed to autografted NP.

The functions of SLI remain obscure. It has been reported that SLI is involved in the longitudinal growth and metabolic maintenance of myelin\(^{27}\) and sodium ion, potassium ion, and chloride ion's cotransportation in the...
peripheral nervous system. Changes of SLI ultrastructure are sensitive indicators of human neuropathies, offering clues to the type of the underlying pathomechanism. An increased number of neuropathic SLIs has been reported in many neuropathic disorders, including in the 7-day NP exposed nerve root in dogs. Because SLI is involved in the cotransportation of ions, pathologic changes in SLI could affect NP exposed nerve root neurophysiologic function, including baseline spontaneous neural activity and mechanosensitivity.

Effects of Fat on Nerve Root
Clinical use of free fat grafts as a barrier to scar formation has been associated with symptomatic neurologic compression mimicking epidural hematoma. Use of a thin piece of fat rather than large thick fat is recommended in human spine surgery. Fat was used in this study as a control to determine the effects of NP on the nerve root. Changes in the spontaneous discharge rate, intensity of ectopic discharges, and mechanosensitivity were not statistically different in fat groups compared to normal nerve root. However, sodium channel density was higher in the fat 21-day group than the normal group. Free fat graft without blood supply might have effects on sodium channel expression in the nerve root after subacute exposure, although the mechanism is not clear. In general, our data suggest that fat may be used as control tissue; the effects of fat on nerve root were different from NP, which had more impact on the nerve root.

Role of Sodium Channels in Neural Activity and Pain
Abnormal accumulation of sodium channels can be found at the tip of injured axons, which increases conductance of voltage-gated sodium channels. Increased conductance of voltage-gated sodium channels can lower voltage threshold rather than pressure threshold so that neurons produce inappropriate ectopic discharges. The hyperexcitability is thought to contribute to spontaneous and movement-evoked neuropathic paresthesias, dysesthesias, and pain. It has been reported that 4 weeks after epidural application of NP, number of rats with antidromically propagated ectopic firings in sural nerve increased. In our study, sodium channel density increased in NP 21-day group without increase of spontaneous baseline discharge rate (Figure 3A). This could be due to blockage of neural signal conduction at neuropathic segment resulting in decrease of total neural activity recorded at the proximal spinal nerve. Further research should be performed to investigate the correlation between increase of spontaneous ectopic discharges and the increase of sodium channel density in NP exposed nerve root.

Rationale for the Pressure Used in This Study
The contact pressure between simulated disc herniations and the deformed nerve root can exceed 400 mm Hg (5.4 g/mm²). Physiologic epidural pressure has been measured in patients with lumbar spinal stenosis in which cauda equina and radicular symptoms are often provoked. The pressure measured ranged between 0.17 to 1.6 g/mm². The threshold pressure in our study ranged from 0.9 to 4.8 g/mm², which was within the range measured in simulated disc herniations.

Clinical Relevance
Findings in this study suggest that nerve roots become sensitive to mechanical compression 7 days after exposure to NP. Mechanical stimulation to the nerve root can provoke abnormal neural activity that can manifest as pain and paresthesia. Mechanical stimulation includes compression from herniated disc and stretch of the nerve root as in the straight leg raising test.

Sodium channel has been found increased with 7-day and 21-day NP exposure in this study. Sodium channel blocking agents including carbamazepine and lidocaine may be useful to alleviate sciatic pain and paresthesia resulting from abnormal neural activity.

Summary
Exposure of nerve root to NP resulted in: 1) potential neural conduction block, higher intensity of ectopic discharges on compression in the acute stage; 2) mechanical sensitization in the acute stage and desensitization in the chronic stage; 3) increase of sodium channel density distributed in axons in the acute and subacute stages; and 4) increased number of axons with neuropathic changes.

Key Points
- Seven days’ exposure of nerve root to nucleus pulposus resulted in potential neural conduction block and higher intensity of ectopic discharges on compression.
- Seven days of nucleus pulposus exposure resulted in mechanical sensitization of nerve root, whereas 42 days’ exposure resulted in desensitization.
- Sodium channel density increased in the axons on the 7th day and 21st day after nucleus pulposus exposure.
- The number of axons with neuropathic changes increased on the 7th day and 21st day after nucleus pulposus exposure.

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