SPINAL CANAL

ANATOMY, PHYSIOLOGY, CLINICAL IMPLICATIONS

Alessandro Marzagalli, PT, ETGOM-GCI lecturer
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STRUCTURES OF THE SPINAL CANAL

- PERIDURAL MEMBRANE (PDM)
- HOFFMAN'S LIGAMENTS
- SINUVERTEBRAL NERVES (SVN)
- DURA MATER
- SYMPATHETIC SYSTEM AND PAIN

PERIDURAL MEMBRANE

PERIDURAL MEMBRANE

- 'PERIDURAL MEMBRANE IS A LITTLE KNOWN FIBROVASCULAR SHEAT LYING EXTERNAL TO THE DURA LINING THE VERTEBRAL CANAL'
- 'IT TRULY SURROUNDS THE DURA, LEAVING A POTENTIAL SPACE BETWEEN IT AND THE DURA, CALLED EPIDURAL SPACE'

SPINE Volume 18, Number 8, pp 1030–1043

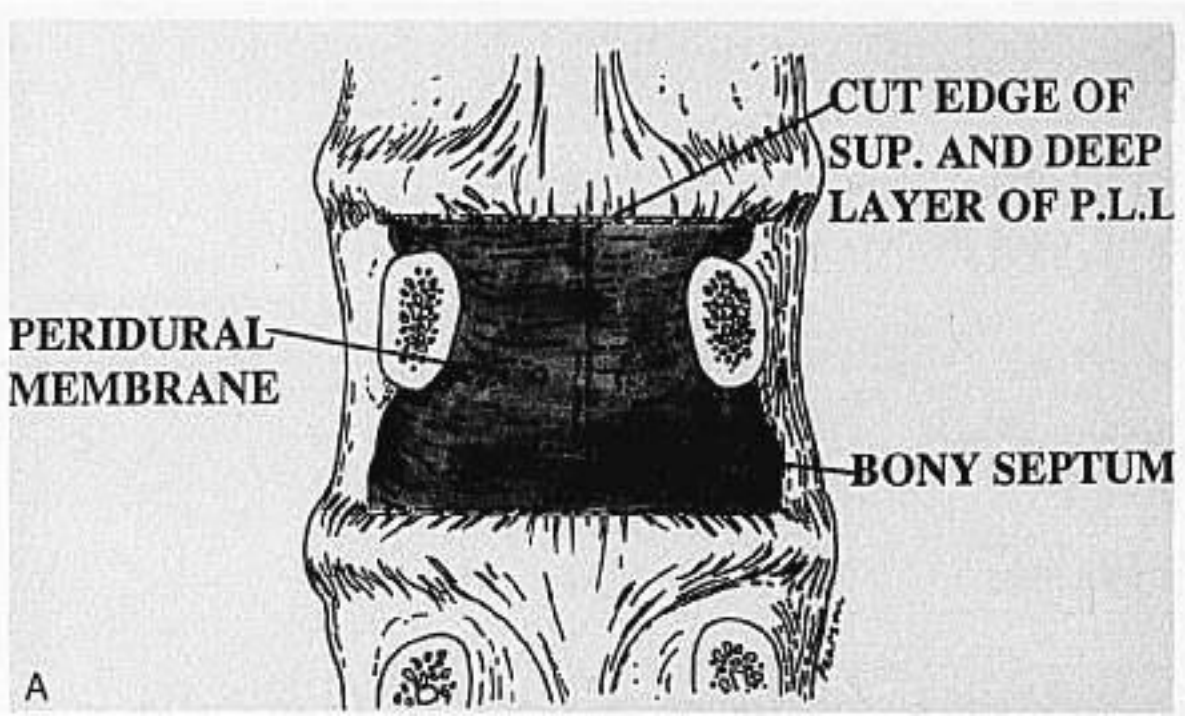
Relationship of the Dura, Hofmann's Ligaments, Batson's Plexus, and a Fibrovascular Membrane Lying on the Posterior Surface of the Vertebral Bodies and Attaching to the Deep Layer of the Posterior Longitudinal Ligament

An Anatomical, Radiologic, and Clinical Study

Leon L. Wiltse, MD, Allen S. Fonseca, MD, James Amster, MD, Paul Dimartino, MD, and Fernando A. Ravessoud, MD

PERIDURAL MEMBRANE

- 1904, FIRST TIME DESCRIBED BY RUDOLF FICK
- 1959 SCHORML AND JUNGHANNS: 'THE HUMAN SPINE IN HEALTH AND DISEASE'
- 1975 DOMMISS: 'ORTHOPEDIC CLINIC OF NORTH AMERICA'

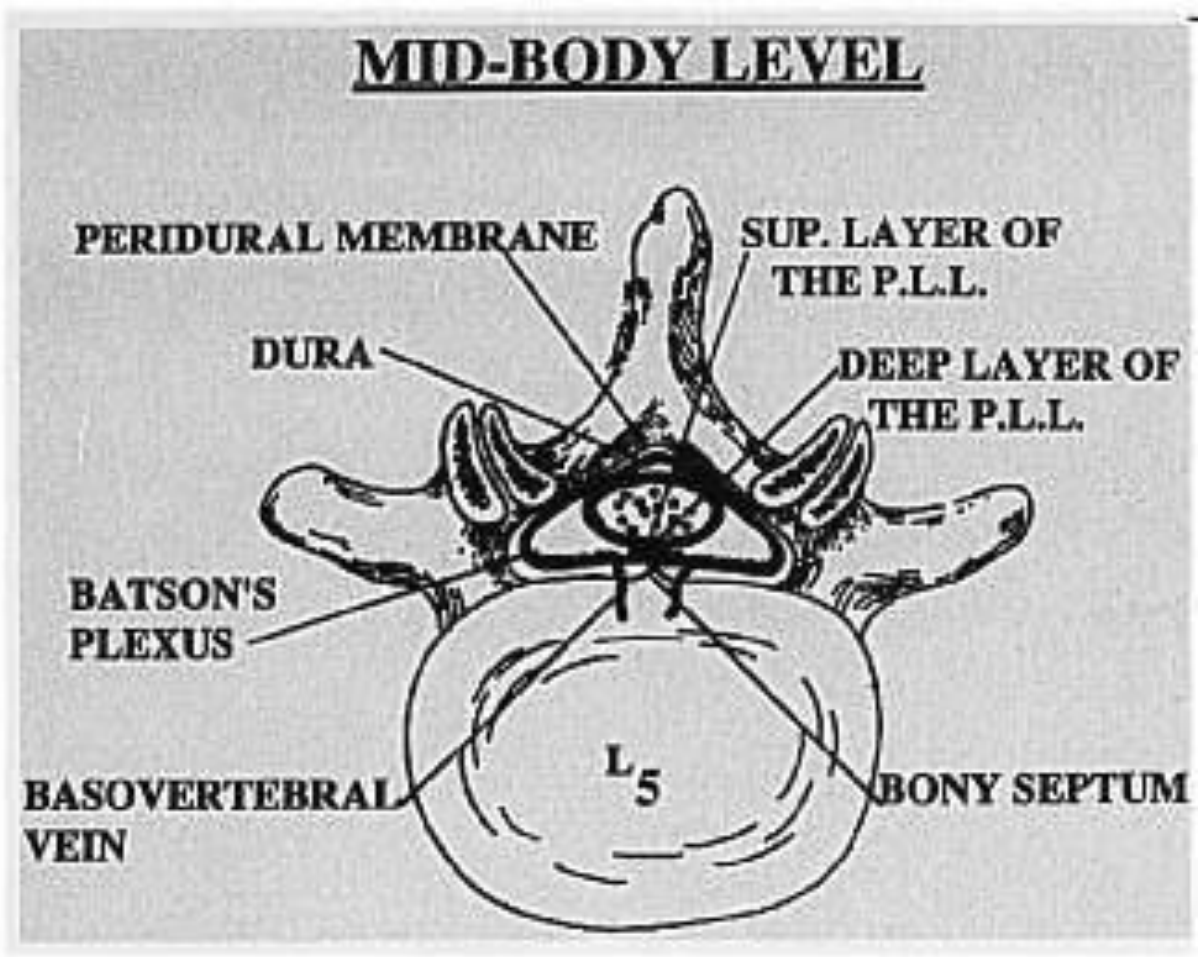


PERIDURAL MEMBRANE

1979

' THE MEMBRANE OF THE SPINAL CANAL':

"surrounding the dura mater, and incorporating the PLL of the spine, is a thick, double layered membrane which at the posterior portion of the spinal canal incorporates the thin periosteal lining of the neural arch. Between its layers are some of the veins of the extradural portion of Batson's plexus…The membrane is one of great dimension and is not generally recognnized as a separate entity. It is generally mistaken as the 'outer layer of the dura'



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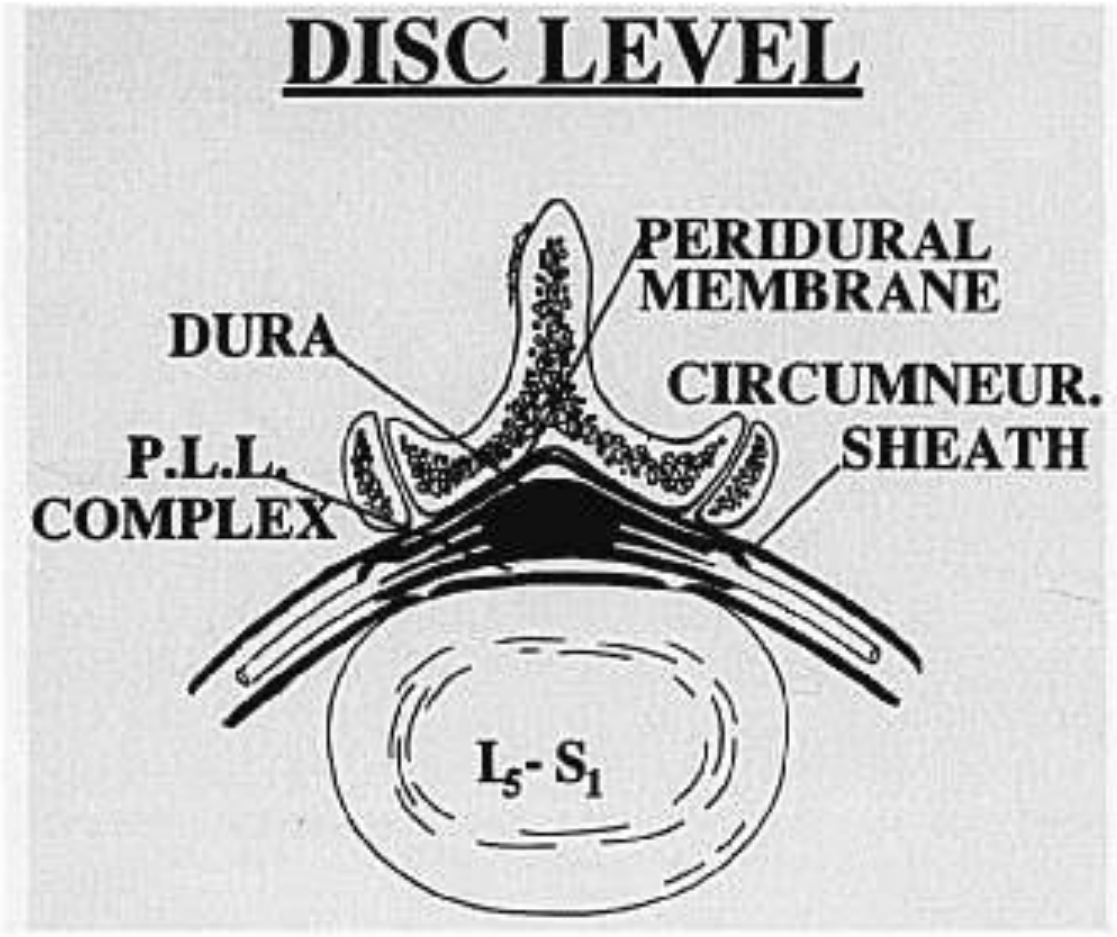
PERIDURAL MEMBRANE

- The peridural membrane surround the entire bony canal.
- It extends out through the lateral vertebral canals surrounding the spinal nerves
- NO peridural membrane on the posterior surface of the annulus



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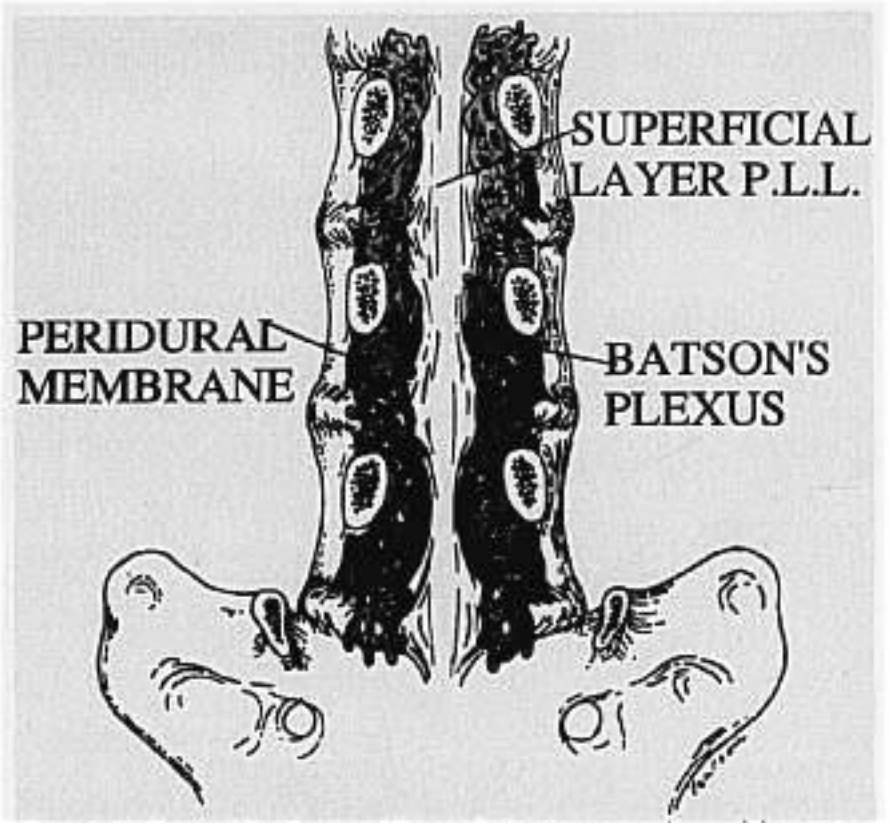
PERIDURAL MEMBRANE

- The peridural membrane only crosses the disc level laterally at the entrance to the bony lateral canal
- The PDM passes under the superficial layer of the PLL and attaches to the undersurface of the deep layer of the PLL
- It appear to be an homolog of the periosteum



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ANATOMY OF THE EXTRADURAL COMPARTMENTS OF THE LUMBAR SPINAL CANAL

Peridural Membrane and Circumneural Sheath

Leon L. Wiltse, MD, FACS

Radiologic Clinics of North America . 2000 Nov;38(6):1177-206.

In all, 40 cadaveric spines were used. Twenty were fresh and 20 were fixed in a formalin mixture.

Age range of the fresh specimens appeared to be between 50 and 72 years.
None was obtained from persons who had died of metastatic disease, infection, or who had prior back surgery.
All fresh specimens had been tested for AIDS and hepatitis.

These specimens were used in the illustrations of our gross anatomic dissections.

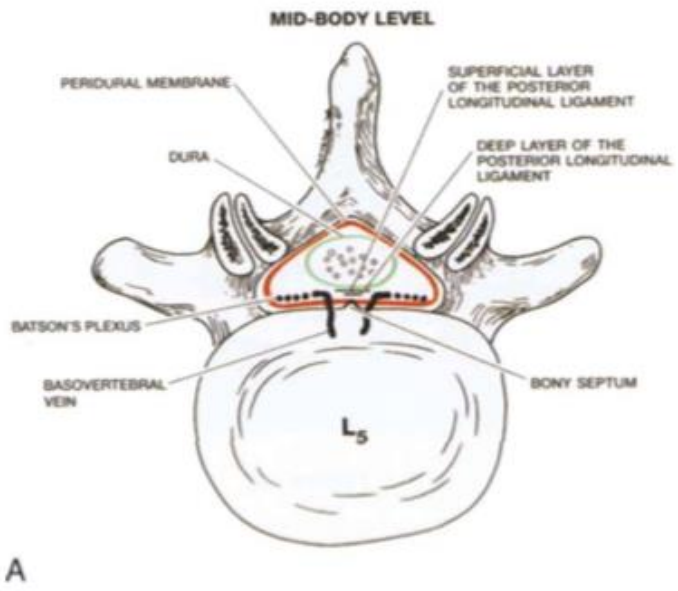
Additional specimens were obtained from a new-born and from an 8-month-old infant.

Through cooperation with our radiology department, a large number of CT scans and MR images were reviewed over the course of several years.

These were compared with anatomic dissections. Dr. Lowell Rogers of the pathology department of the Long Beach Memorial Hospital performed the microscopic anatomy and the other work with the infants.

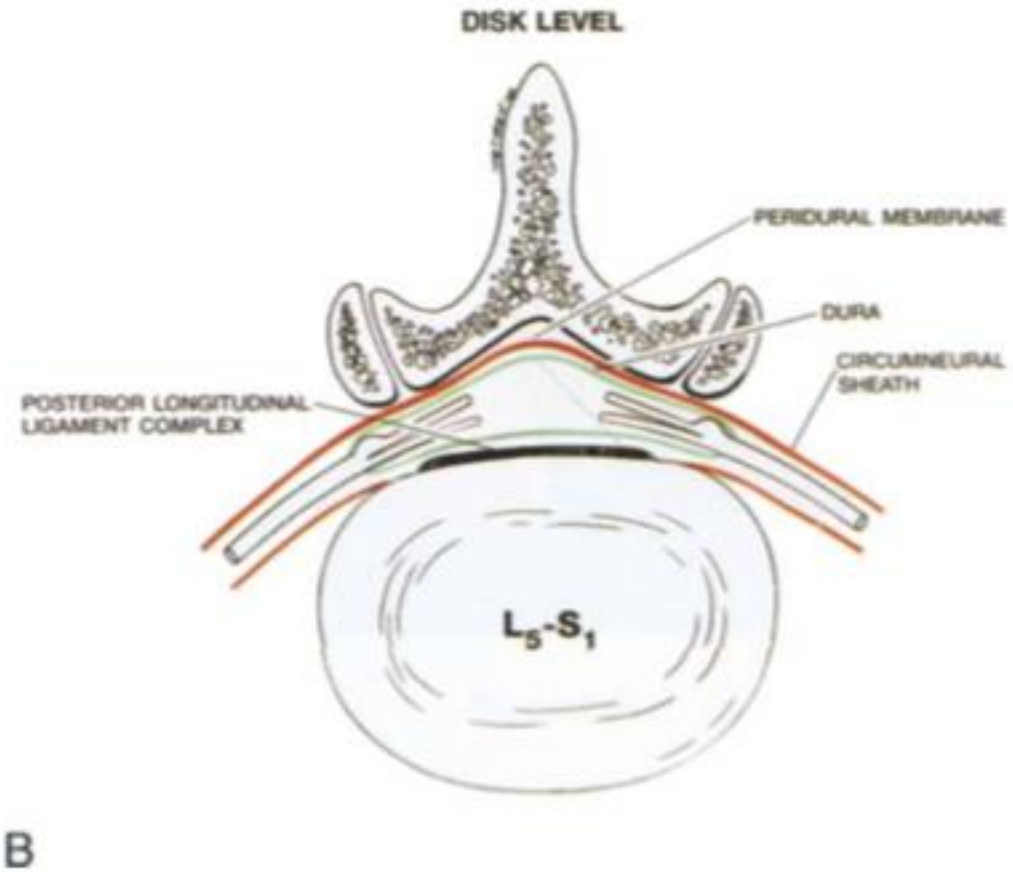
The Peridural Membrane

If in dissection one approaches the lumbar spine from the posterior with the cadaver on its abdomen the first bony structures to be seen are the spinous processes and then the laminae. If the undersurfaces of the laminae are examined carefully, one finds a very thin glossy membrane that is very securely attached to the lamina. This is the **peridural membrane** at its posterior part behind the dura. It encircles the dura.



Notice that the peridural membrane surrounds the entire bony canal.
In front, the veins of Batson lie in the body of this membrane and on its posterior surface. In the central area they can be followed into the nutrient foramina through the basivertebral veins.

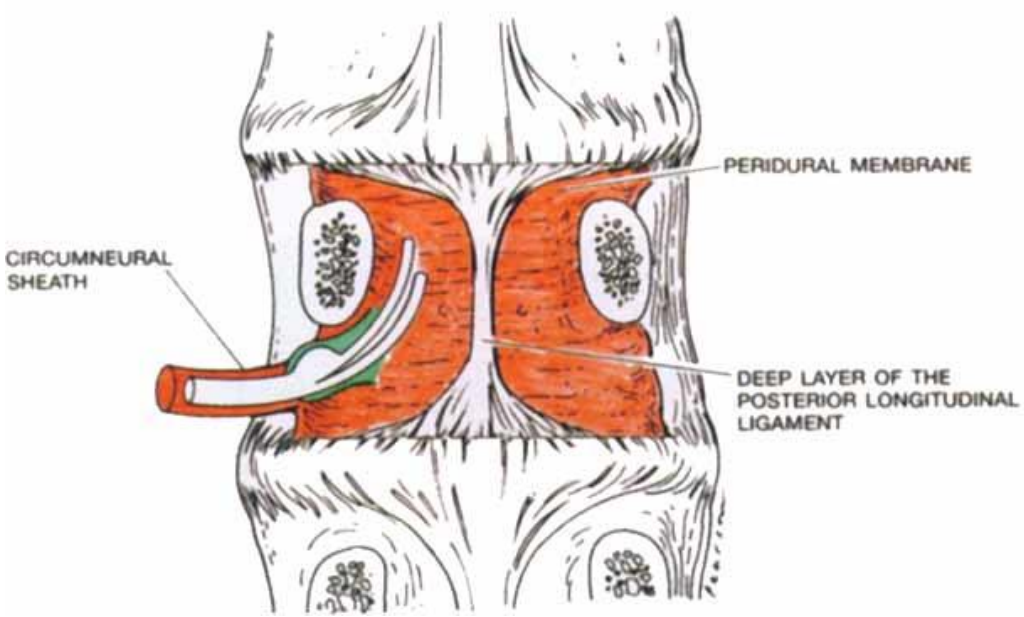
As can be seen in the drawing, the peridural membrane surrounds the dura. The potential space between it and the dura is the **epidural space**. The potential space between it and the bone of the vertebral body is the **premembranous space**. This membrane is attached posteriorly not only to the undersurfaces of the laminae but also to the undersurfaces of the ligamentum flavum. It is a homologue of the periosteum but is thinner and more delicate than most periosteum.

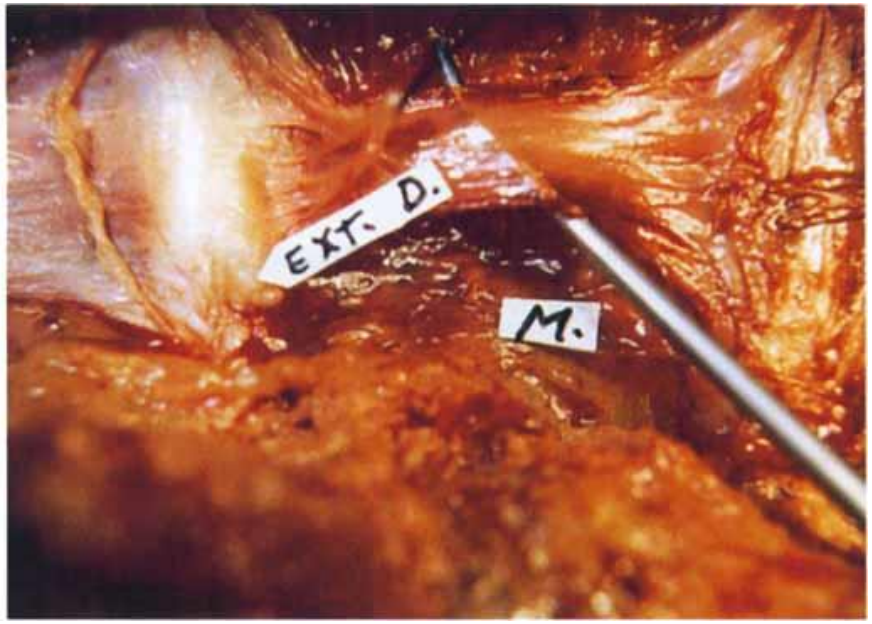


Color Fig. B shows a cross section at the level of the L5-51 disk.

This is typical of other disk levels in the lumbar spine. Notice that no peridural membrane is shown on the posterior surface of the annulus. The inner surfaces of the pedicles are covered with this membrane but the outer or lateral surfaces are covered with typical periosteum

As the membrane swings around onto the posterior surface of the vertebral body, it lies on the bone but is not attached to the bone. There is a potential space between it and the back of the vertebral body.
At the cephalic and caudal ends it goes deep to the deep PLL and along with it and the superficial PLL attaches to the borders of the disk-annulus complex





The dural root sleeve *(green)* passes out from the dura into the lateral foramen.
It consists of a sleeve of dura surrounding two roots, a sensory and a motor.
Immediately beyond the ganglion, the two roots combine and form a typical mixed peripheral nerve.
At that same point, the dural sleeve becomes tightly adherent to the nerve and becomes the epineurium.

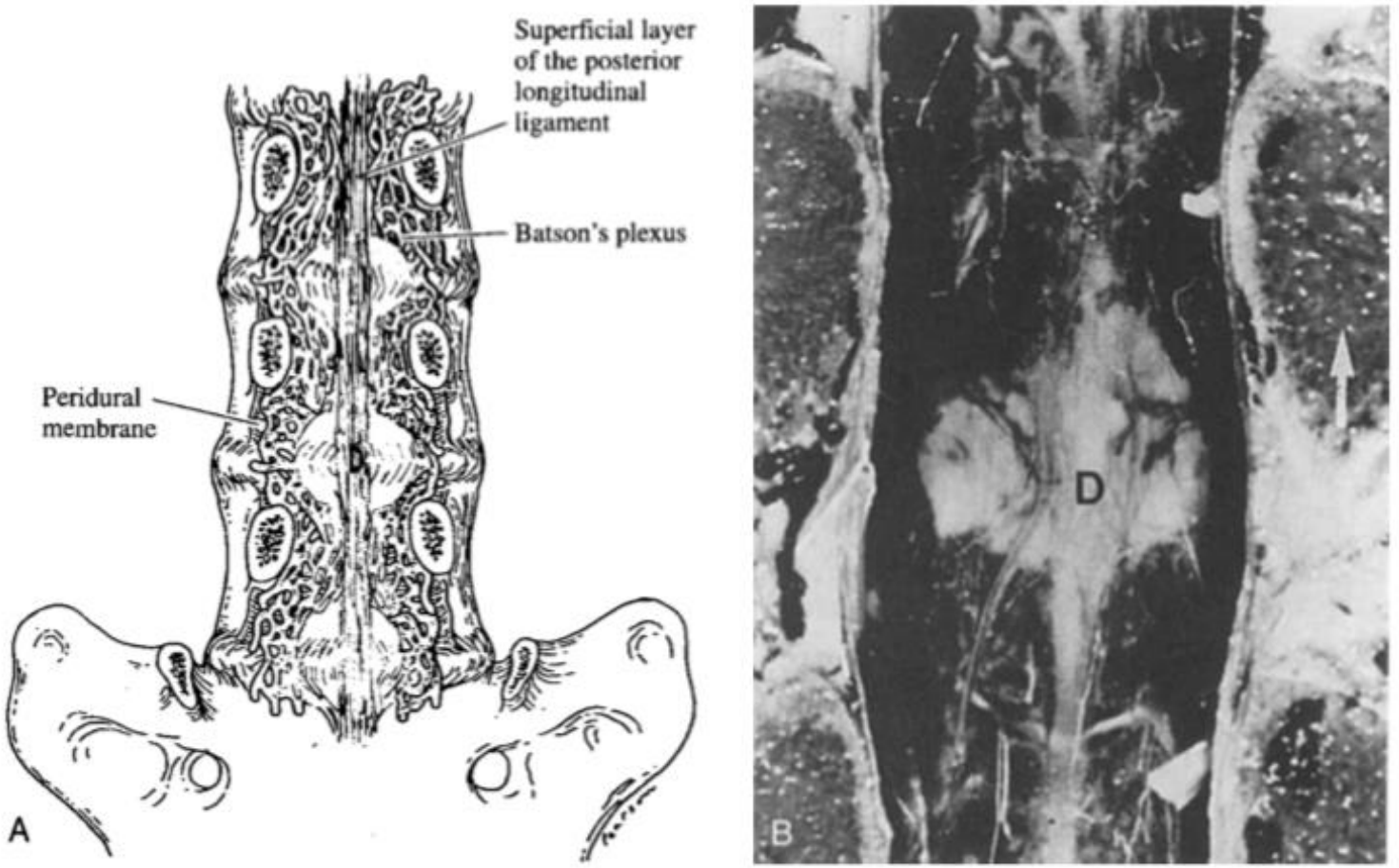
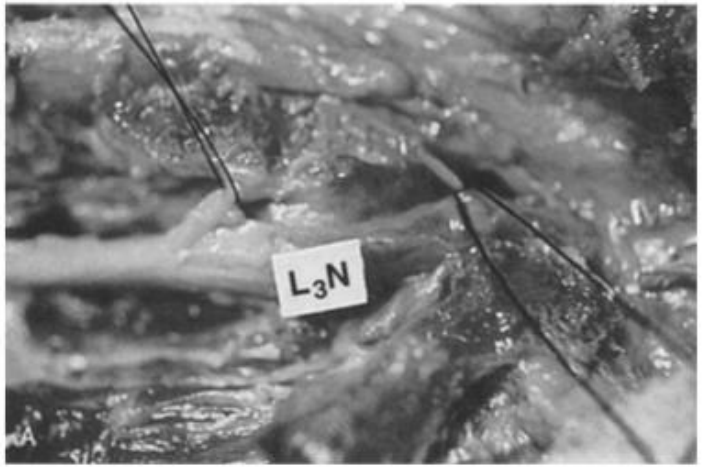


Figure 7. *A*, Lower spine with posterior elements removed. Note that Batson's plexus lies on the peridural membrane but continues over the PLL and the disk space. Note also that the veins cross the annulus far laterally but widen out and nearly come together over the back of the vertebral body. *B*, India ink was injected into the center of a vertebral body. The ink came back through the basivertebral veins, through the nutrient foramen and into the Veins of Batson. (Courtesy of Prof. Harry Crock, London, England.)

Ligaments of the Lateral Neurovascular Canals of the Spinal Vertebrae

Although a complete discussion of the ligaments in the lateral vertebral canals is beyond the scope of this article. it is important to note that the ligaments tether the circumneural sheath and the nerve to the bony canal. Inside the sheath are many lesser fibrils and vessels that keep the nerve from sliding.
There are distinct transforaminal ligaments about 1 mm in diameter passing from the pedicle to the nerve, which are consistently found.

On straight-leg raising the slip of a given nerve in a lateral canal is no more than 1 or 2 mm. If much more slip were permitted, the vessels would be stretched so much they could not function.



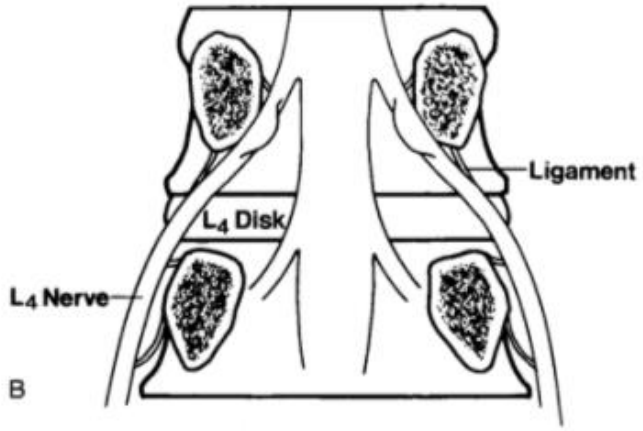


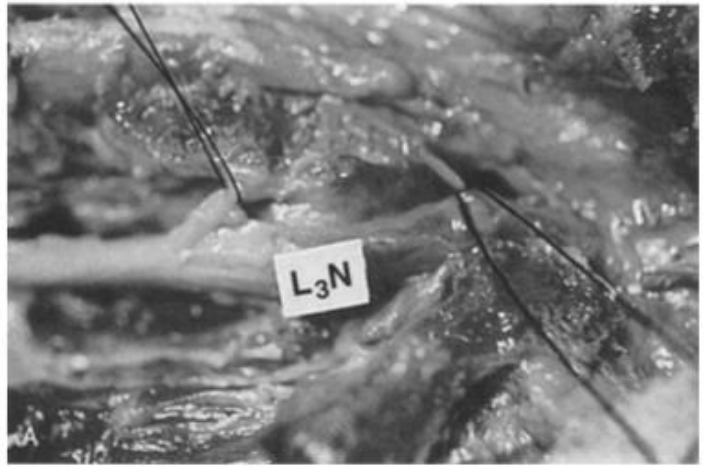
Figure 11. Left L3 nerve as it comes out of the lateral canal. Notice one ligament marked by a black thread goes from the upper and medial part of the pedicle cranialward and attaches to the epineurium of the nerve. The other ligament, marked also by a black thread, starts at the lateral and caudal part of the pedicle and passes distally to attach to the nerve. The thread on the left passes across the cut end of the pedicle of L4 and the thread on the right across the pedicle of L3. L3N = L3 spinal nerve. The circumneural sheath has been largely removed on the picture. To the right is cranial and to the left, caudal. *B*, Arrangement of the ligaments that pass from the pedicle to the nerve. Note the more distal (or caudal) ligament protects the cauda equina roots from severe jerks on the leg and the more cranial ligaments protect from traction in either direction.

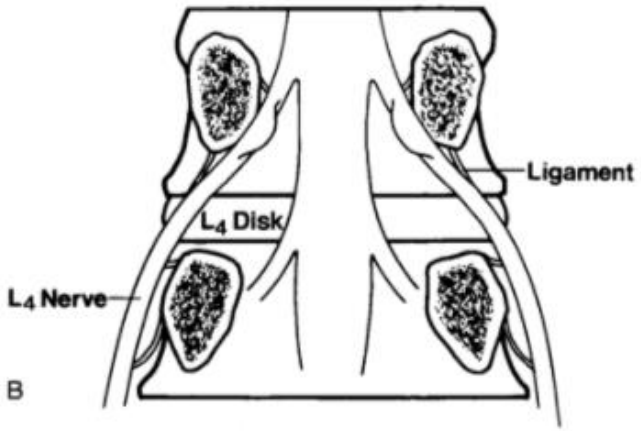
Illustration continued on opposite page

Ligaments of the Lateral Neurovascular Canals of the Spinal Vertebrae

The situation with the L5 spinal nerve is unique. After it exits the intervertebral fora- men it passes through a tunnel formed by the sacral ala posteriorly and the lumbosacral ligament (the sickle ligament) anteriorly (Figs. llC and *D)*. Notice that the L5 nerve passes through a V-shaped opening. This is a fre- quent source of compression of the L5 nerve. When pedicle screws are used, if they are driven straight in and on through the anterior cortex of the ala, they very likely hit this nerve. Because the nerve is so tightly bound

down, penetration of as little as 3 to 4 mm may compress the nerve enough to cause motor paralysis Figure show the sickle ligament cut and the nerve reflected first down then up to show how small ligaments tether the nerve to the large sickle ligament.





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Ligaments of the Lateral Neurovascular Canals of the Spinal Vertebrae

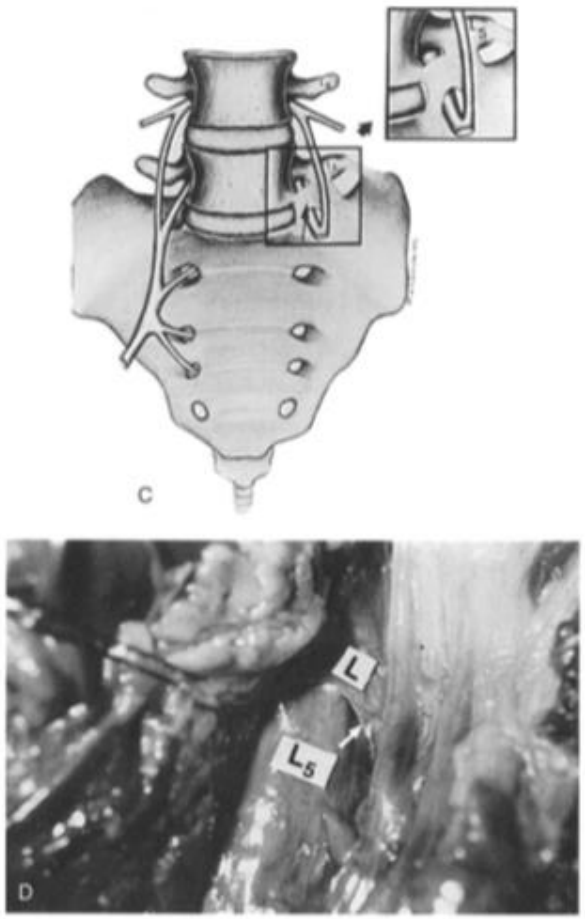


Figure 11 *(Continued). C,* Anterior surface of the sacrum and lower lumbar vertebrae showing the sickle ligament and the L5 nerve. The *arrow* points to the sickle ligament (lumbosacral ligament). *D,* Lumbosacral ligament (sickle ligament of Danforth) *(arrow)* and L5 nerve at the anterior aspect of the sacral ala. Note the ligament arches over the L5 nerve. This ligament is present only at L5 and causes this nerve to be much more susceptible to injury.

Illustration continued on following page

The situation with the L5 spinal nerve is unique. After it exits the intervertebral fora- men it passes through a tunnel formed by the sacral ala posteriorly and the lumbosacral ligament (the sickle ligament) anteriorly (Figs. IIC and *D).* Notice that the L5 nerve passes through a V-shaped opening. This is a fre- quent source of compression of the L5 nerve. When pedicle screws are used, if they are driven straight in and on through the anterior cortex of the ala, they very likely hit this nerve. Because the nerve is so tightly bound down, penetration of as little as 3 to 4 mm may compress the nerve enough to cause motor paralysis

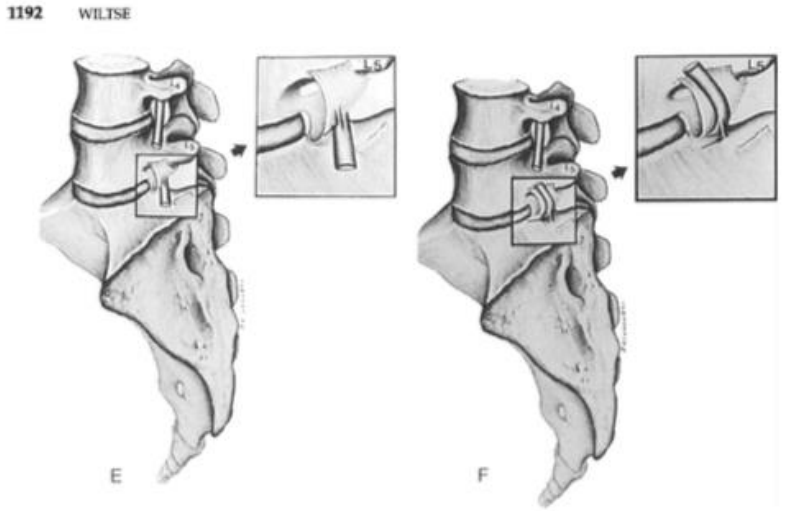


Figure 11 *(Continued). E,* Left side of the lumbosacral area. The sickle ligament has been partially cut through and the nerve is reflected downward. Note the small ligaments binding the nerve to the ligament. *F,* Left side of the lumbosacral area with the sickle ligament reflected upward and the nerve reflected upward. Note the small ligaments binding the nerve to the ala. (*From* Wiltse LL: The intervertebral foramina. *In* Watkins RG, Collins JS Jr (eds): Lumbar Diskectomy and Laminectomy. Rockville, MD, Aspen Publications, 1987, p 213; with permission.)

REVIEW ARTICLE

The Peridural Membrane of the Spinal Canal: A Critical Review

Saeed Ansari, MD[*,†]; James E. Heavner, DVM, PhD, FIPP (Hon)[*,‡]; Douglas J. McConnell, BHS[†]; Hassan Azari, PhD[†,§]; Hemmo A. Bosscher, MD*

[*]Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, Texas, U.S.A.; [†]Department of Neurosurgery, University of Florida, Gainesville, Florida, U.S.A.; [‡]Cell Physiology and Molecular Biophysics, Texas Tech University Health Sciences Center, Lubbock, Texas, U.S.A.; [§]Department of Anatomical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

Table 1. Original studies of membranous tissue surrounding the spinal canal

Author	Year	Type of study	Nomenclature	Description
Frykholm[5]	1951	Cadaver dissection	Epidural membrane	Dorsal: Two thin layers of fibrous tissue enveloping a single row of veins Ventral: Fascial membrane separating dura from venous plexuses
Dommisse[7]	1975	Cadaver dissection	Not specified	The PLL extends circumferentially, lining the spinal canal along with the periosteal membrane of the neural arches
Dommisse[2]	1975	Cadaver dissection	PM	A thick, double-layered membrane that incorporates the periosteum of the neural arches at the posterior portion of spinal canal
Hayashi[3]	1977	Cadaver dissection with histology, including fetal study	Epidural membrane	Deep PLL continues laterally as a tough membrane, lining the intervertebral foramen, merging with the ALL Superficial PLL extends laterally as a membrane of variable consistency and is continuous with the thin epidural membrane of the ventral epidural cavity
Hasue[25]	1983	Cadaver dissection	Epidural membrane	Noted a membranous structure in the posterior spinal canal between the dura and the ligamentum flavum This membrane was continuous with the "epiradicular sheath," which was in turn continuous with the superficial membrane of the PLL
Schellinger[14]	1990	Clinical study with MRI, including cadaver dissection with histology	Lateral membrane	Delicate, translucent membrane extending from the lateral edge of PLL to the spinal canal wall. The posterior surfaces of the vertebral bodies and the lateral membranes delineate the anterior epidural space containing the retrovertebral veins
Hogan[19]	1991	Cadaver study (cryomicrotome sections)	Not specified	Observed a membranous separation extending from the PLL, which created an anterior epidural space filled with veins Also noted a thin, brown, fibrous layer on the anterior aspect of the ligamentum flavum, which at times was continuous with the epineurium of dorsal root ganglia
Wiltse[13]	1993	Cadaver dissection	PM	Fibrous tissue one-fourth the toughness of the dura lines the vertebral canal (includes pedicles, laminae, and ligament flava) Batson's plexus lies posterior to its anterior extensions Does not cover the intervertebral disc Envelops spinal nerves through lateral spinal canals Attaches to the anterior surface of the deep PLL Observed no periosteum along the inner spinal canal. The PM acts as a homologous tissue
Kumar[15]	1996	Immuno-histochemical study (rats)	PM	Abundant mast cells and nerve fibers exist within the PLL and PM Similar elements not abundant in cervical and lumbar dura
Loughenbury[24]	2006	Cadaver dissection	PM	Noted the presence of two membranes within the anterior spinal canal The first is the previously described PM, observed in all specimens The second ("superficial membrane of the PLL") was observed in 6 of 18 cadavers and covered only the posterior surface of the superficial PLL

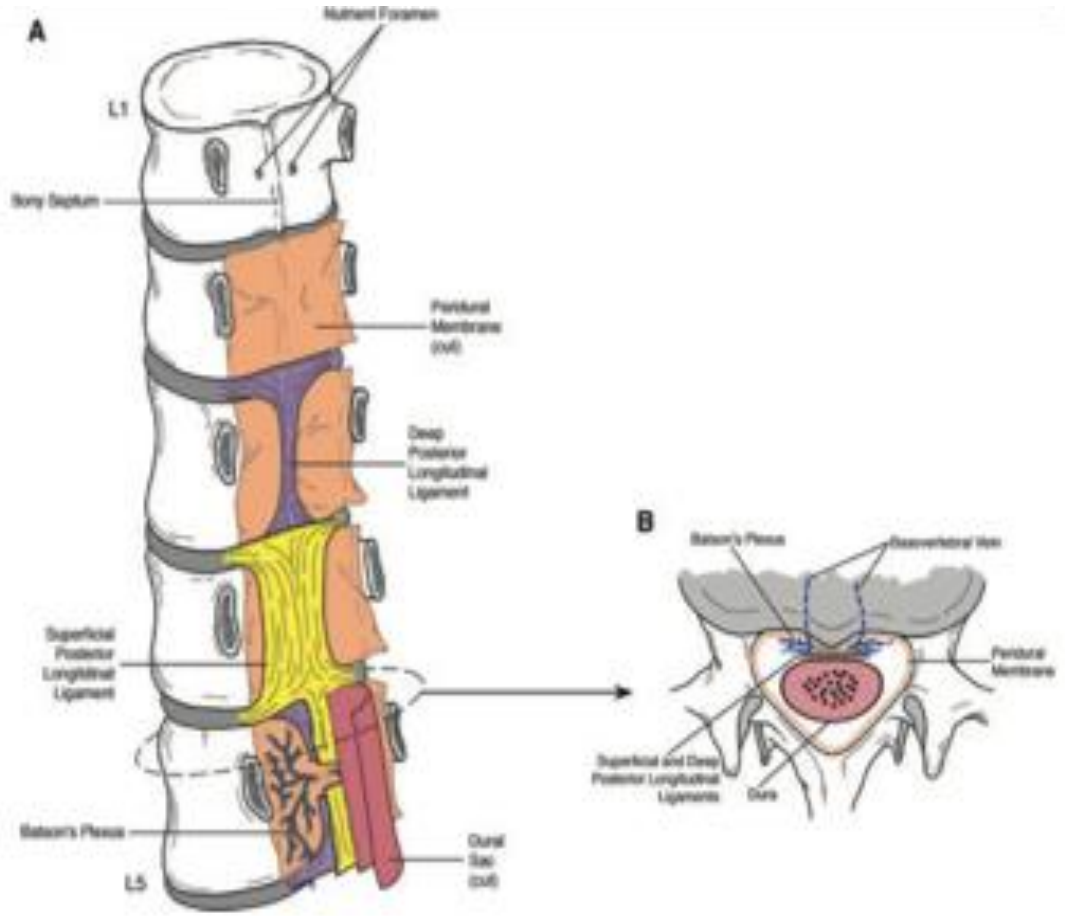
PM, peridural membrane; PLL, posterior longitudinal ligament.

The most proven function of the PM involves demobilization of foreign material into the epidural cavity. Almost 40 years ago, Frykholm mentioned that in cases with disc herniation, the connective tissue in the anterior spinal canal "protects the cord from local compression." This notion imparts great functional significance to the PM. This has been well documented in cases of intervertebral disc herniation, when fragments of the nucleus pulposus emerge from within the annulus fibrosus in a posterior direction.

Schellinger highlighted that fragments rarely mobilize beyond the anterior epidural space, bordered posteriorly by the "lateral membranes." **Because of its relatively small width, the PLL could not contain these fragments on its own. Thus, the PM would play a vital role in stabilizing nuclear material and keeping it out of the main epidural cavity.**

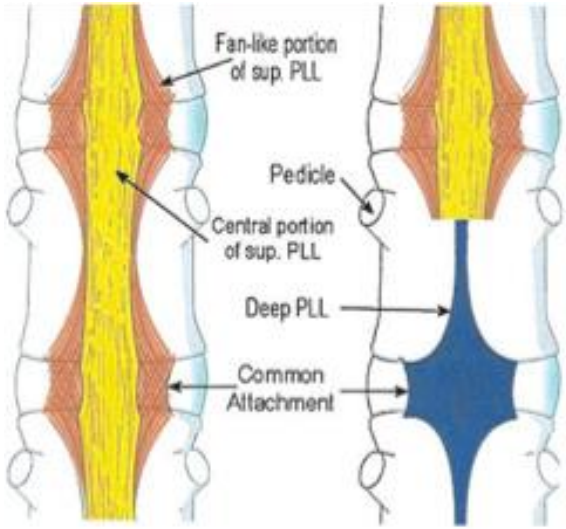
These more straightforward roles of the PM share some similar mechanisms with its subtle, complicated manifestations related to the protection of spinal contents. The separation of the epidural cavity into compartments, readily identified by epidurography, also offers some protection from the spread of pathologies of the spine

The PM may also act as a barrier in the opposite direction, retaining leaked cerebrospinal fluid (CSF) within the epidural cavity.



Sequential progression of connective tissue layers in the anterior spinal canal from anterior to posterior (L1–L5, posterior view, pedicles cut). The peridural membrane (PM) is visualized anterior to the posterior longitudinal ligament and Batson's plexus, but does not cross the level of the intervertebral disc. (B) Axial cross section of spinal column at L5 vertebra, showing the PM lining the inner surface of the spinal canal and the position of adjacent structures.

Kumar et al. had restated the hypothesis that although there could be numerous sources of pain in the spinal canal, the PLL and PM could become symptomatically involved as adhesions or iatrogenic fibroses develop between these structures and other spinal contents. If these were then subjected to traction forces, such as those that exist during disc herniations, the PM could relay nociceptive signals.



Clinical Anatomy 19:487–492 (2006)

ORIGINAL COMMUNICATION

The Posterior Longitudinal Ligament and Peridural (Epidural) Membrane

PETER R. LOUGHENBURY, SHARAN WADHWANI, AND ROGER W. SOAMES*

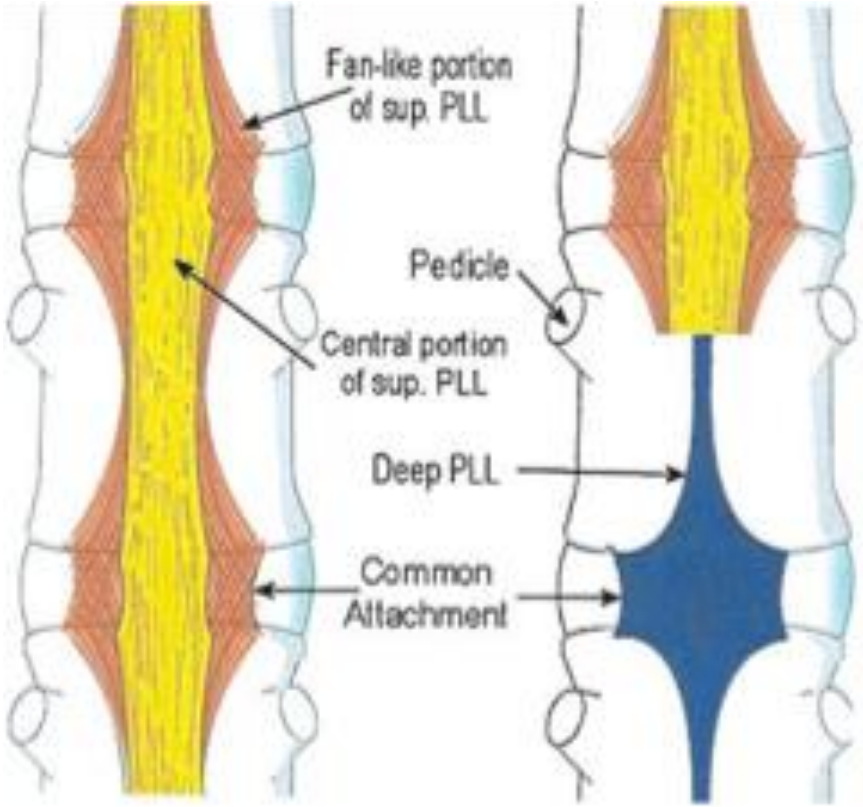
School of Biomedical Sciences, University of Leeds, Leeds, UK

PERIDURAL MEMBRANE AND PLL

PERIDURAL MEMBRANE AND PLL

A continuous, well-developed peridural membrane covering the posterior aspect of the vertebral body anterior to the deep layer of the PLL was observed in all specimens

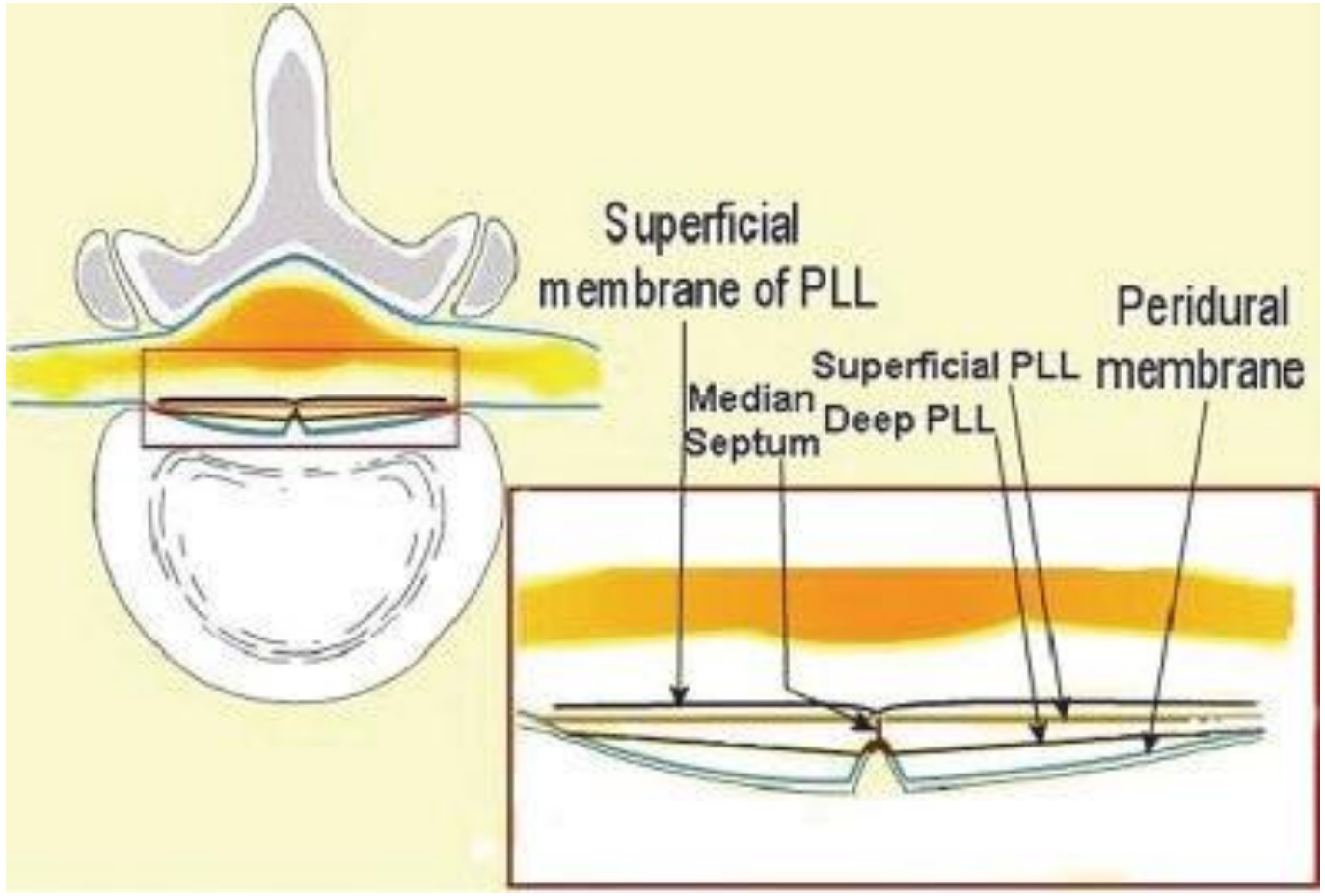
The membrane attached to the pedicles and extended laterally to cover the spinal nerves as they exited from the vertebral canal.



PERIDURAL MEMBRANE AND PLL

It is unclear whether the "superficial membrane of the PLL" represents one of the three layers of the PLL reported by both Plaisant et al. (1996) and Mercer and Bogduk (1999).

The interlacing fibers of the IVD and PLL made it difficult to identify the precise attachment of the peridural membrane, although fibers appeared to attach to the pedicles and lateral borders of the IVD.



INNERVATION OF THE PERIDURAL MEMBRANE

There is evidence that low back pain may originate from a peridural membrane (PDM) at the inferior and medial aspect of neural foramen of the lumbar spine.

The peridural membrane in human is well innervated and contains sensory nociceptive nerve fibers suggestive of a nociceptive function of the membrane.

THE ANATOMICAL RECORD 299:484–491 (2016)

The Peridural Membrane of the Human Spine is Well Innervated

HEMMO A. BOSSCHER,* JAMES E. HEAVNER, PETAR GROZDANOV, IRFAN A. WARRAICH, MITCHELL S. WACHTEL, AND JANET DERTIEN
Texas Tech University Health Sciences Center, Lubbock, Texas

INNERVATION OF THE PERIDURAL MEMBRANE

In the spine, formation of venous channels separates the peridural membrane from dura mater to form the epidural cavity and the epidural venous plexus with which the membrane is closely associated (Ansari et al., 2012; Newell, 1999).

The membrane has been shown to protect the contents of the bony vertebral canal from intrusion of foreign material (Ansari et al., 2012)

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INNERVATION OF THE PERIDURAL MEMBRANE

All but one of the samples contained a moderate or marked number of PGP9.5 positive fibers indicating that the peridural membrane is a well-innervated structure.

Presence of CGRP and SP positive nerve fibers and demonstration of small unmyelinated nerve fibers using electron microscopy, suggests that these fibers have nociceptive function.

This is consistent with epiduroscopy findings (Bosscher and Heavner, 2013) as well as pain relief obtained by percutaneous ablation and curettage of the intervertebral foramen (PACIF) in humans with chronic low back pain (Bosscher and Heavner, 2015).

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The most important finding in this investigation is that the human PDM exists and is a unique anatomical structure.

It may be defined as a continuous and complete peridural connective tissues sheath that envelops the neural elements in the spinal canal and neural foramen.

The membrane contains the epidural venous plexus and the peri-neural evagination of this plexus into the neural foramen. The PLL may be regarded as a condensation of dense fibrous connective tissue within the PDM

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DOI: 10.1002/ar.24476

ARTICLE

The Anatomical Record WILEY

The anatomy of the peridural membrane of the human spine

Hemmo A. Bosscher[1,2,3,8] | Petar N. Grozdanov[4] | Irfan I. Warraich[5] | Clinton C. MacDonald[6] | Miles R. Day[7,8]

Results of this investigation indicate that the PDM is a continuous anatomical structure, that is, there are no interruptions in the membrane.

On microscopic examination, both superficial and deep portions of the PLL are continuous with the connective tissue of the PDM.

Thus, the PLL could be regarded as a condensation of dense fibrous tissue within the PDM (Chaynes et al., 1998; Dun, 2006; Frykholm, 1951; Hamid et al., 2002; Hayashi et al., 1977) covered dorsally by the thin translucent outer layer of the PDM. This outer layer corresponds well with the superficial layer described by Loughenbury (Loughenbury et al., 2006)

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The Anatomical Record WILEY

The anatomy of the peridural membrane of the human spine

Hemmo A. Bosscher[1,2,3,8] | Petar N. Grozdanov[4] | Irfan I. Warraich[5] | Clinton C. MacDonald[6] | Miles R. Day[7,8]

PDM and periosteum are distinct and separable tissues, a finding in accordance with reports by others (Ansari et al., 2012). Indeed, unlike PDM, periosteum is not a continuous structure, that is, it does not cover the intervertebral disc or ligamentum flavum.

In addition, the histology of periosteum and PDM differ. Confusion is not surprising as PDM and periosteum may be viewed as the spinal equivalent of the cranial epidural veins and endosteum (Ludinghausen von, 1967; Stringer, 2012) and are embryologically and anatomically closely related (Ansari et al., 2012; Hamid et al., 2002; Munkacsi, 1990; Sensenig, 1949).

In contrast to the spinal canal, in the neural foramen PDM and periosteum are not connected (Ansari et al., 2012; Breit et al., 2013; Hayashi et al., 1977; Wiltse, 2000)

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It was recently demonstrated that the PDM of the human spine is a well-innervated structure and contains nociceptive fibers (Bosscher et al., 2016).

Trauma or degeneration of the disc or facet joint may lead to release of tissue breakdown products into the suprapedicular compartment. Accumulation of inflammatory mediators may cause inflammation, activation of nociceptors and pain originating from the suprapedicular PDM. This protective mechanism may be essential for the proper functioning of the spine under conditions of strain. In clinical studies, inflamed appearing suprapedicular PDM was painful when touched with an epidural endoscope (Bosscher & Heavner, 2014) and mechanical disruption of thin suprapedicular PDM resulted in resolution of back pain (Bosscher & Heavner, 2015) .

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HOFMANN'S LIGAMENTS

The Epidural Ligaments (of Hofmann): A Comprehensive Review of the Literature

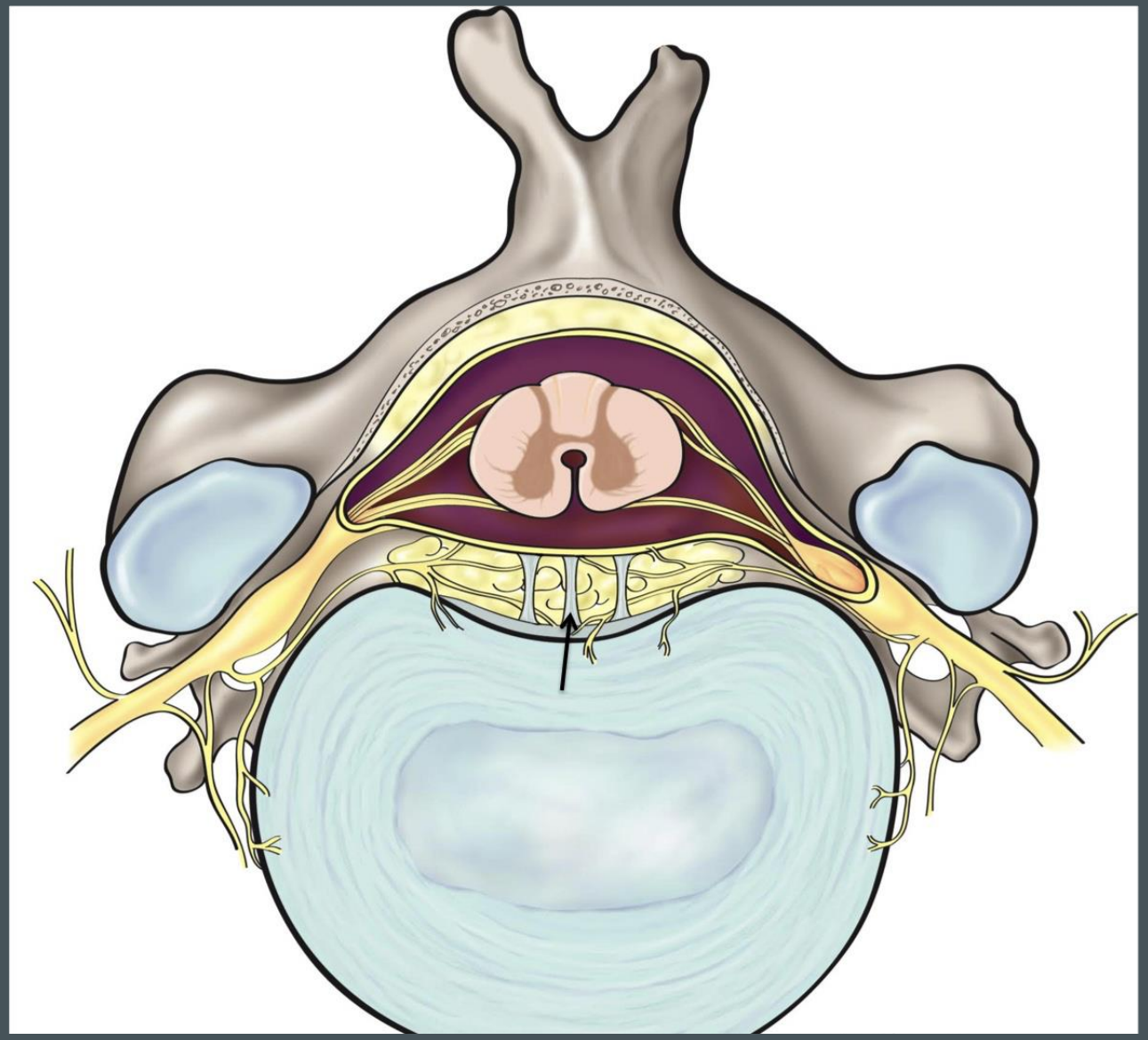
Gabrielle G. Tardieu [1], Christian Fisahn [2 3], Marios Loukas [4], Marc Moisi [5 6], Jens Chapman [7], Rod J. Oskouian [8], R. Shane Tubbs [9]

HOFMANN'S LIGAMENTS HAVE BEEN DESCRIBED AS FIBROUS CONNECTIVE TISSUE BANDS THAT RUN VENTROLATERALLY FROM THE DURA MATER TO THE VERTEBRAL CANAL .

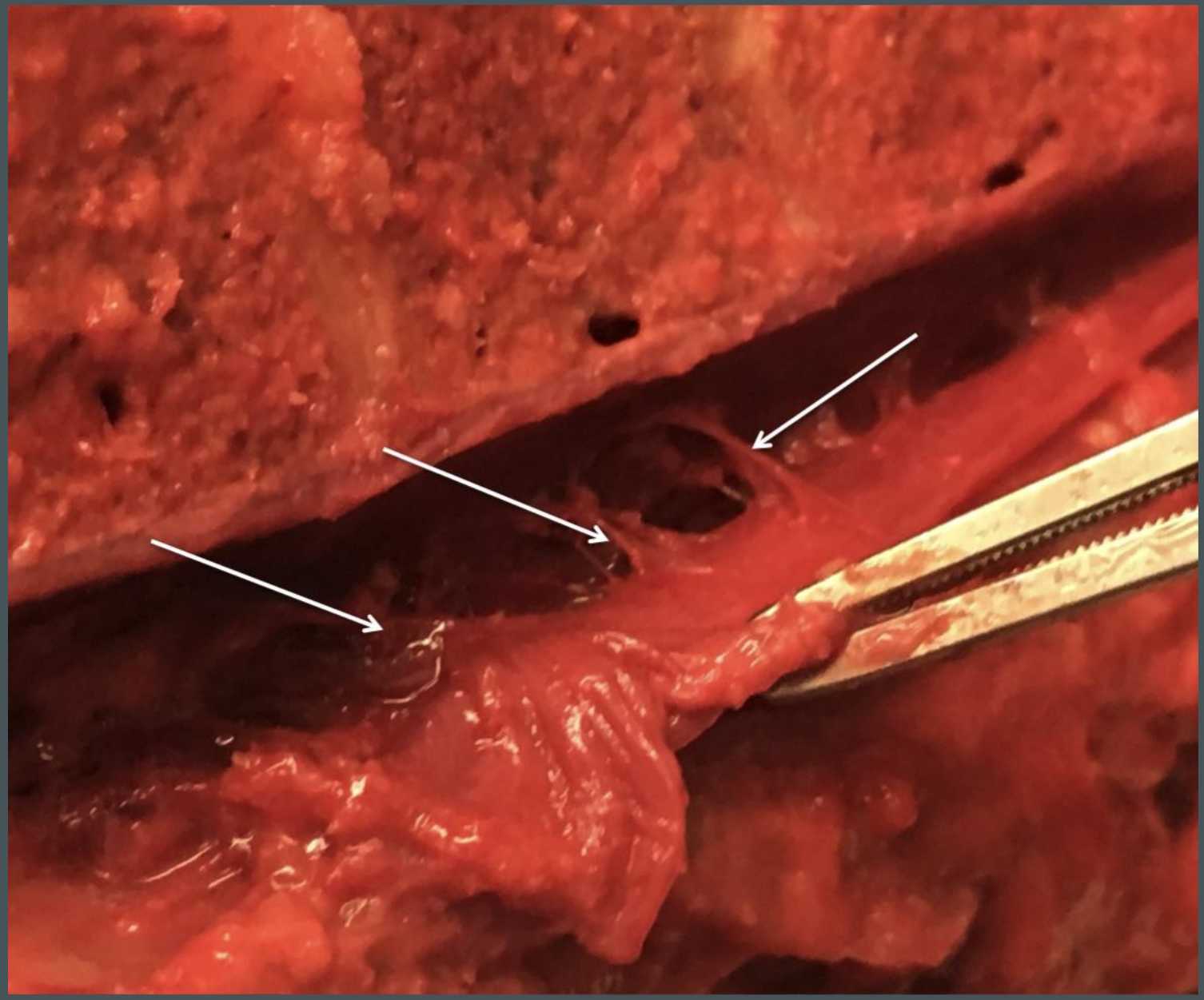
TROLARD (1893) HAD REPORTED THESE LIGAMENTS EARLIER AND RESTRICTED THEM TO THE LOWER LUMBAR SPINE AND UPPER SACRAL CANAL

HOWEVER, IN 1898, MAX HOFMANN DEFINED THESE BANDS IN DETAIL .

ACCORDING TO WILTSE, ET AL. (1993) AND WILTSE (2000) , HOFMANN'S LIGAMENTS HAVE BEEN SEEN TO BE "NARROW, ALMOST THREADLIKE" CONNECTIONS BETWEEN THE DURAL SAC AND THE PLL, BEING PRESENT AT MOST LEVELS



FRESH CADAVERIC DISSECTIONS NOTING HOFMANN'S LIGAMENTS (ARROWS) HERE ATTACHING ANTERIORLY TO THE PLL.



HOFMANN'S LIGAMENTS

There were three sets of Hofmann's ligaments based on their connections;

1) midline (from anterior dural sac to PLL),
2) lateral (from anterolateral dura to the lateral extent of the PLL) and
3) proximal root sleeve (from the dural extension of the nerve root sleeve to the PLL and periosteum of the inferior pedicle.

True Hofmann's ligaments included only the midline and lateral ligaments as the proximal root sleeve attachments were not acknowledged by Hofmann.

HOFMANN'S LIGAMENTS

The orientation of Hofmann's ligaments was seen to be consistent, running in a caudocranial fashion from the dura to the PLL at cervical and upper thoracic levels while in the lumbar vertebrae, a craniocaudal orientation was present. The ligaments at T8 to T9 lay almost at right angles between the dural sac and the PLL and became more oblique nearing the ends of the spine. This arrangement of these ligaments suggests a supportive and protective role in stabilizing and anchoring the dural sac and by that, the spinal cord and spinal nerves, to the bony vertebral canal.

HOFMANN'S LIGAMENTS

The connection of the anterior dura mater to the PLL by Hofmann's ligaments produces further support for the dural sac, with Hofmann's ligaments securing it near to the posterior surface of the vertebral bodies and intervertebral discs. The presence and function of Hofmann's ligaments are in agreement with the statement that the dural sac does not collapse after death, even when there is no longer any support from the cerebrospinal fluid pressure, which, more or less, does not exist in the cadaver

HOFMANN'S LIGAMENTS EMBRYOLOGY

This is congruent with the statement of Hamid, et al. (2002) that Hofmann's ligaments are present at birth.

During initial growth, the PLL is closely adhered to the anterior dura mater.

HOFMANN'S LIGAMENTS PROPOSED FUNCTION

One proposed function of Hofmann's ligaments, early in development, is to keep the dura against the vertebrae as the spine lengthens. When the intervertebral disc places pressure on the anterior dural sac, Hofmann's ligaments may also play a protective role in limiting movement of the spinal nerves posteriorly preventing stretching of the spinal nerve roots , and thereby pain . On the contrary, Munkácsi reported clinical and anatomical studies, which indicated that the epidural ligaments contributed to the pathogenesis of nerve root compression in the sciatica syndrome, originally caused by herniated discs in the vertebral canal. Wiltsle stated that with the prevention of movement of the spinal nerves, pain is produced due to the pressure anteriorly, although there is sufficient space posteriorly for the nerve in the bony canal.

Wadhwani, et al. and Spencer, et al. (1983) posited that Hofmann's ligaments may contribute to the pathogenesis of sciatica due to stress on an attached nerve root, as well as cause somatic pain by pulling on the PLL. This theory is supported by the fact that the degree of the protruded intervertebral disc and the severity of the neurological symptoms do not always match.

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Review Article

Anatomy of the posterolateral spinal epidural ligaments

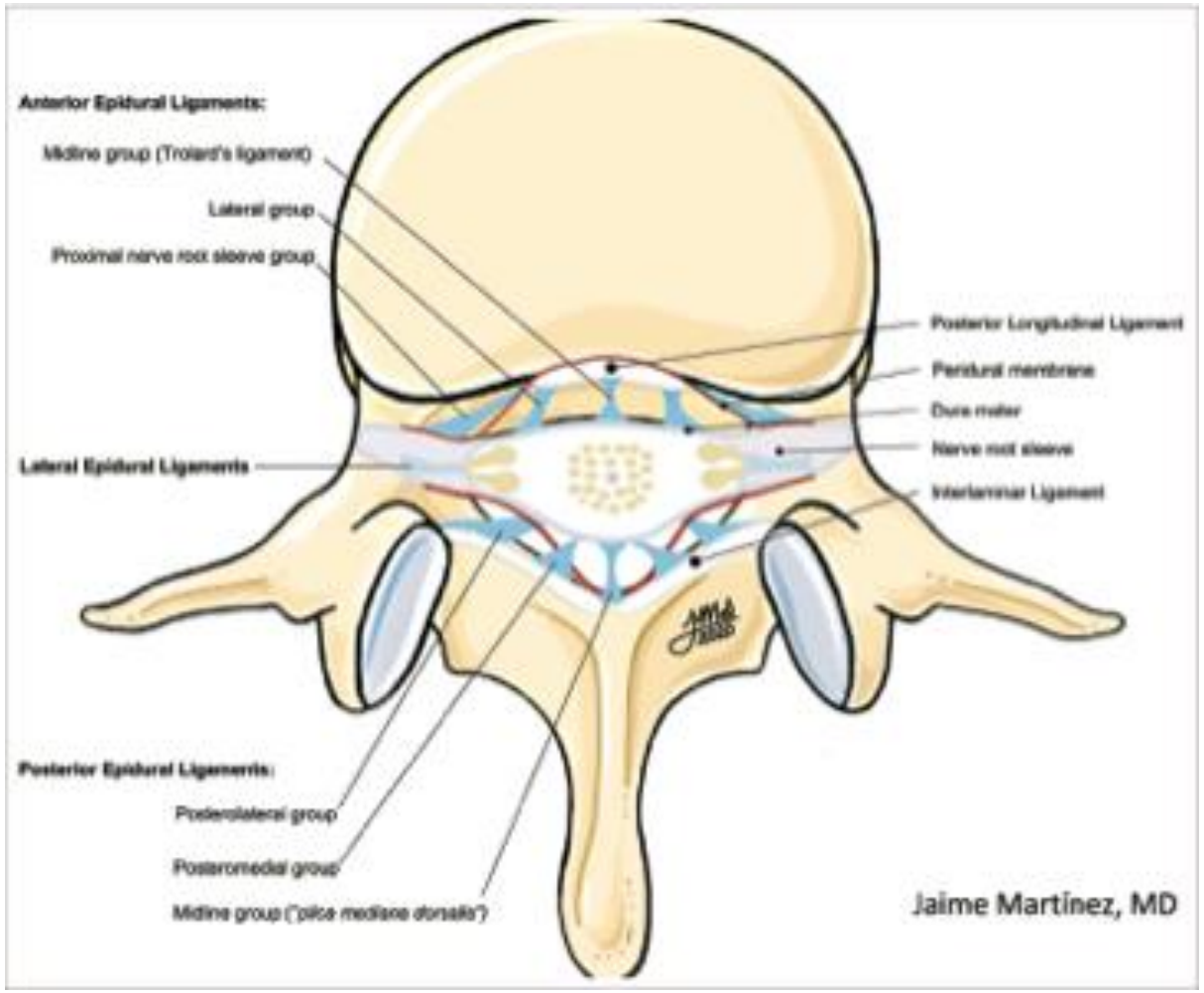
Jaime L. Martinez Santos[1,2], Stephen P. Kalhorn[1]

EPIDURAL LIGAMENTS

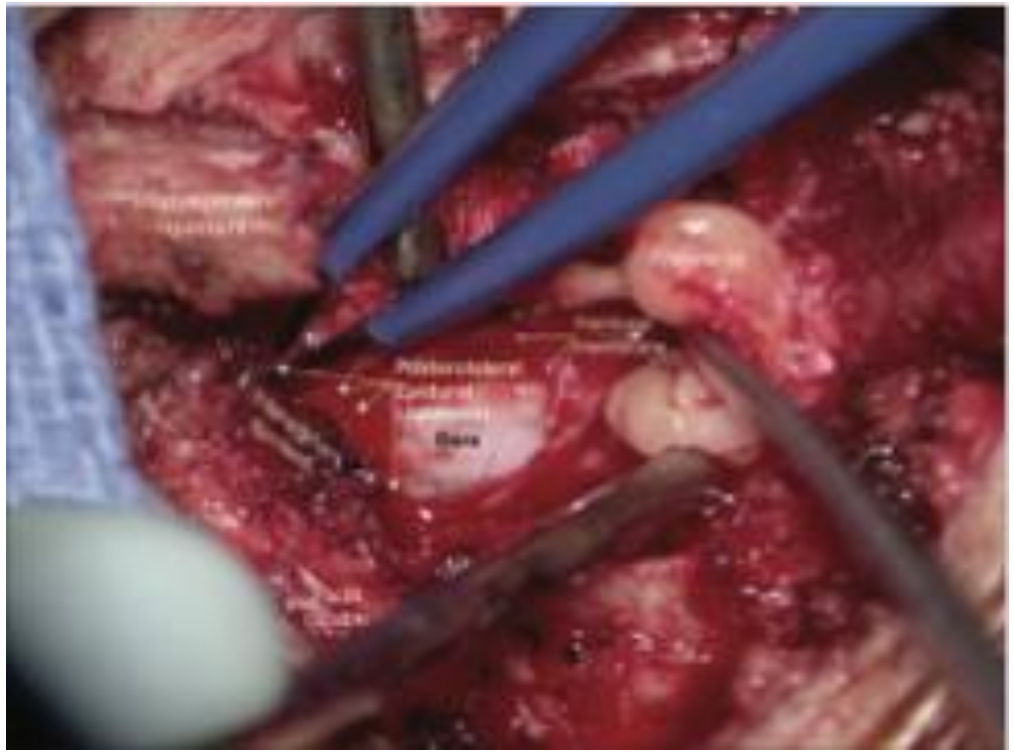
The spinal posterolateral ELs and their anatomic relationships with the peridural membrane (PDM) and insertions on the ipsilateral interlaminar ligament (ligamentum flavum), vertebral lamina, and medial zygapophyseal facet capsule.

Table 1: Epidural or meningovertebral ligaments.

Anterior (or Ventral) epidural ligaments (Hofmann's)
Lateral epidural ligaments
Posterior (or Dorsal) epidural ligaments
• Midline group (Trolard's ligaments): originate on the ventral dura and insert on the PLL
• Lateral group: Originate on the ventrolateral dura and insert on the lateral border of the PLL
• Proximal nerve root sleeve group (not initially described by Hofmann) originate on the lateral dura, ventral to the nerve root sleeve, and insert anteriorly on the PLL and inferior pedicle
• Originate on the lateral dura, at the level of the nerve root sleeve and insert on the pedicle
• Midline group ("Plica mediana dorsalis"): originate on the dorsal dura and insert on the lamina and interlaminar ligaments, bridging the midline gap between the interlaminar ligaments
• Posteromedial or dorsomedial group: Originate on the dorsal dura and insert on the ipsilateral interlaminar ligament and lamina
• Posterolateral group: originate on the posterolateral dura (dorsal to the nerve root sleeve) and insert on the ipsilateral vertebral lamina, interlaminar ligament and zygapophyseal joint capsule



THESE ANATOMICALLY VARIABLE LIGAMENTS ARE PRESENT AT MOST SPINAL LEVELS, AND ANCHOR THE THECAL SAC CIRCUMFERENTIALLY, NOT ONLY VENTRAL TO THE NERVE ROOTS AS INITIALLY DESCRIBED BY HOFFMANN



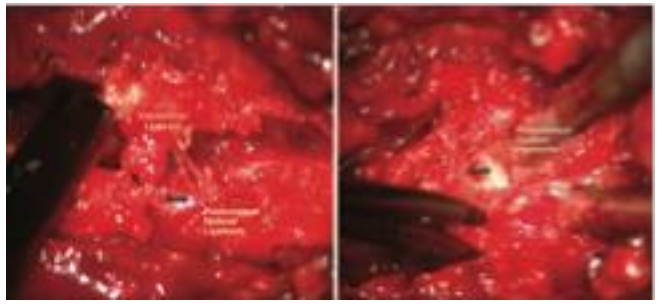
12-YEAR-OLD MALE WHO UNDERWENT A LUMBAR LAMINECTOMY FOR SPINAL CORD DETETHERING. INTRAOPERATIVE PHOTOGRAPH AFTER PERFORMING AN L4 LAMINECTOMY AND REMOVING THE INTERLAMINAR LIGAMENT. □E DURA IS EXPOSED, AND THE EPIDURAL FAT IS MOBILIZED CAUDALLY ON THE LEFT SIDE TO IDENTIFY THE PERIDURAL MEMBRANE VENTRAL TO IT AND THE POSTEROLATERAL EPIDURAL LIGAMENTS ATTACHING LATERALLY ON THE FACET CAPSULE AND INTERLAMINAR LIGAMENT.

The PDM divides the epidural space into two virtual spaces:
(1) theouterorexternalepiduralspace(betweenthePDMand the walls of the spinal canal) and
(2) the inner epidural space (virtual space between the PDM and dura).

Tributaries to the internal epidural venous plexus of Batson and epidural fat attach dorsally and are embedded within the PDM and may track along the ELs.
Epidural hemostasis can be achieved by identifying this thin layer of ELs, and gently holding it away from the dura between the blades of the bipolar electrocautery.

SPONDYLOSIS AND FACET ARTHROPATHY MAY CEMENT POSTEROLATERAL ELS TO THE DURA

Patients with advanced spondilosys, stenosis and facet arthropathy may develpop prominent posterolateral Els that firmly adherent to the dura, attributed to a local inflammatory response. At surgery, a Kerrison rongeur or the foot plate attachment of a high speed drill may inadvertently grasp these ELs, causing their avulsion at site of dural insertion. Therefore, at surgery, ELs should be sharply divided or cut (avoiding undue traction) to allow for mobilization the thecal sac and nerve roots as in performing a discectomy.



A 60-year-old male patients who underwent a lumbar laminectomy for neurogenic claudication. (a and b), intraoperative photographs after rongeur bites to the left L3 lamina and interlaminar ligament (a) and left-sided medial facet (b) showing how the posterolateral ligament is cemented to the posterolateral dura and inserts on the lamina, interlaminar ligament and medial facet capsule. Note that forceful traction on these fragments could inadvertently cause a durotomy

SINUVERTEBRAL NERVES

Review Article
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Anatomy & Cell Biology

A comprehensive review of the sinuvertebral nerve with clinical applications

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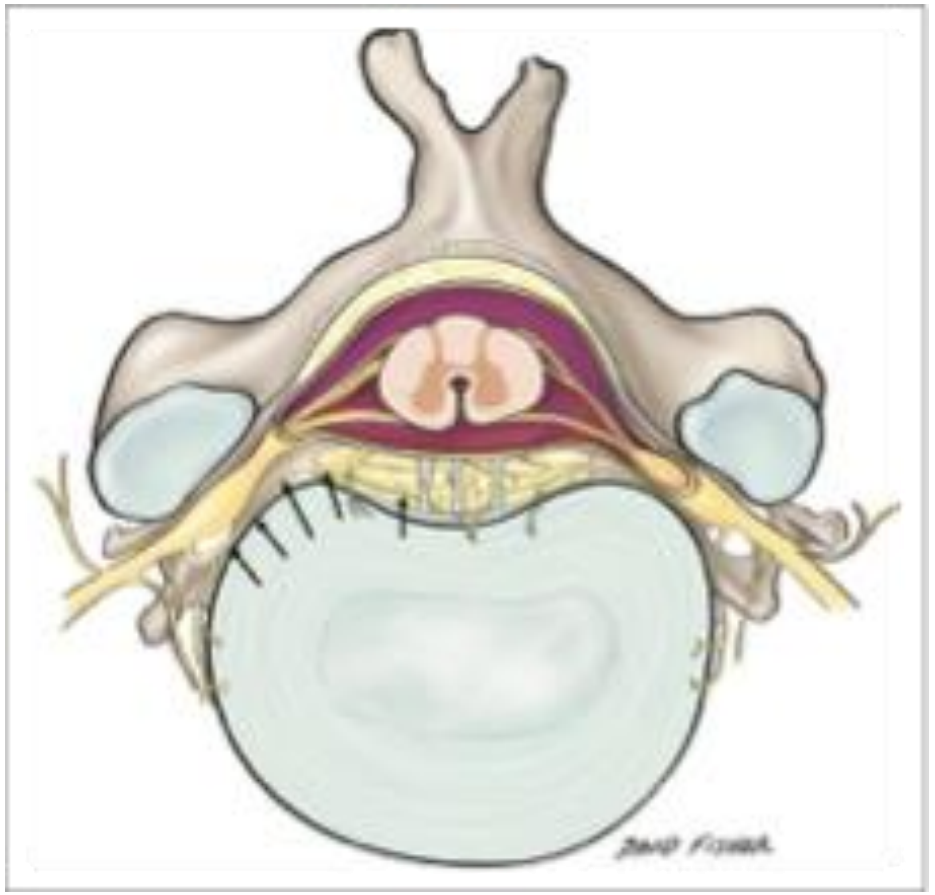
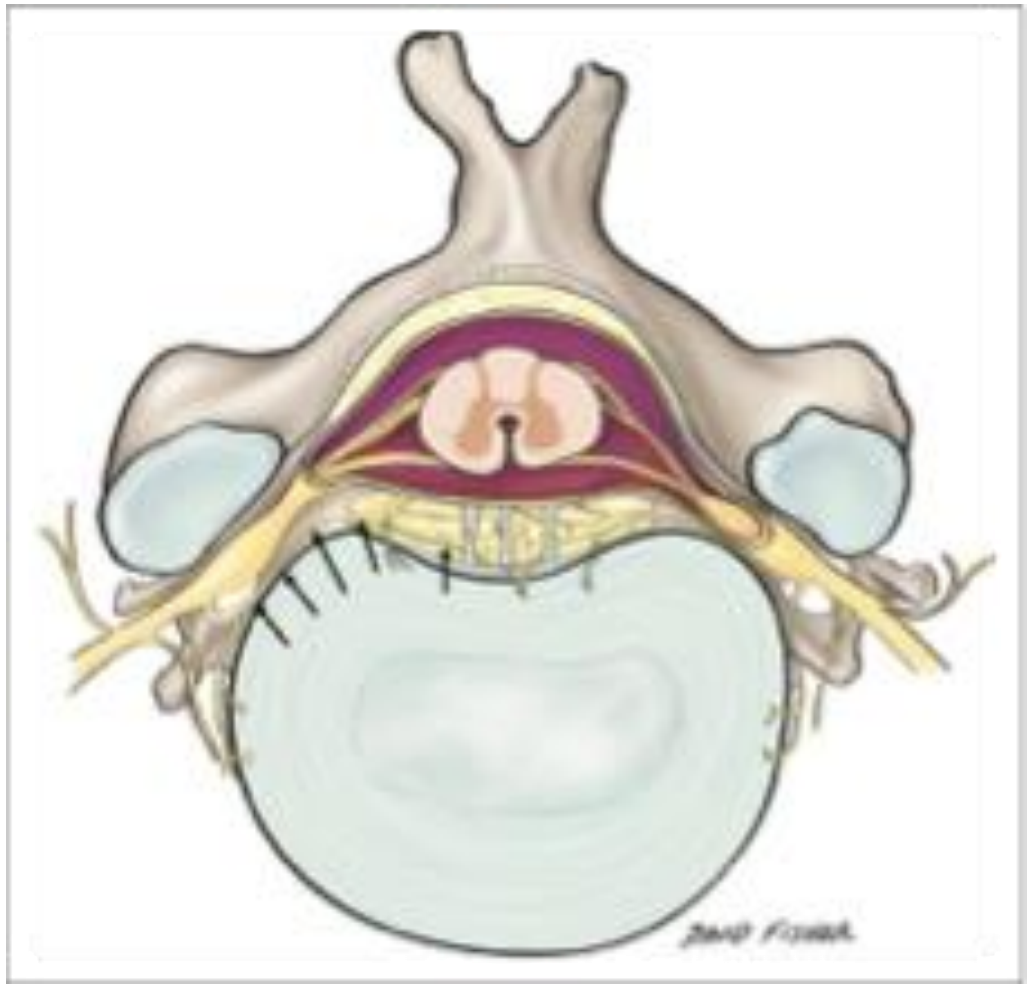


Sinuvertebral nerve (arrows) taking a recurrent course and re-enters the spinal canal through the intervertebral foramen.

First described by the German anatomist Hubert von Luschka in 1850, the sinuvertebral nerve has since acquired many other names including the recurrent nerve of Luschka, recurrent meningeal nerve, ramus meningeus, and meningeal branch of the spinal nerve

Luschka described the sinuvertebral nerve's derivation from the spinal nerve and its connection to the sympathetic nervous system.

It is debated whether the distribution of the sinuvertebral nerve is segmented at the level of the spinal nerve, or non-segmented with branches extending both rostrally and caudally within the spinal canal. Van Buskirk described it as extending the length of the vertebral canal, with anastomosing branches above and below it. Lazorthes et al. challenged those findings, describing the nerve's course as **purely segmental**.



Since the nerve is both somatic and autonomic, it has been investigated to determine whether it conveys discogenic pain via general visceral afferents or somatic afferents

More recently, Cavanaugh et al. attempted to answer this question by stimulating the posterior surface of the L5–L6 intervertebral disc in rabbits using electrical and mechanical methods of neuronal excitation.

After dissecting each grey ramus communicans, Cavanaugh et al. established the general visceral afferents as the predominate pathway in lumbar discogenic pain.

According to anatomy textbooks, the sinuvertebral nerve is formed by the union of a somatic root from the ventral ramus and an autonomic root provided by the grey ramus portrayed as a single nerve, but more accurately it comprises a series of fine filaments of which one to four larger trunks can be evident

The sinuvertebral nerve arises bilaterally from the ventral ramus of each spinal nerve just distal to the dorsal root gan- glia, supplying both proprioceptive and nociceptive fibers.
Upon separation from the ventral ramus, it travels medially for 2–3 mm to be joined by a branch from the grey ramus communicans. This branch contributes sympathetic neurons to the sinuvertebral nerve.

The nerve then takes a recurrent course and re-enters the spinal canal through the intervertebral foramen, more specifically through the osteofibrous foramen formed by the deep anterior intraforaminal ligament, just caudal to the pedicle.
Although it passes through the intervertebral foramen, it is unlikely to be compressed during disc herniation because it is located alongside the pedicle, cranial to the corresponding disc.
At the point of entrance, the composite nerve is about 0.5–1.0 mm in diameter

Findings based on work by Imai et al. using immunoreactive staining for tyrosine vasoactive intestinal polypeptide and substance P demonstrated. **postganglionic sympathetic fibers in the posterior longitudinal ligament**

Additionally, work by Konttinen et al. and Coppes et al. using calcitonin gene-related peptide and substance P, showed the presence of **nociceptive fibers in both superficial and deep divisions of the sinuvertebral nerve as it courses along the posterior longitudinal ligament.**
Moreover, tyrosine hydroxylase immunoreactive staining responded only to the superficial network, verifying Kojima's and Nakamura's previous findings that the **superficial network was primarily sympathetic.**

The next innovation in the investigation of the sinuvertebral nerve involved the use of retrograde transport markers cholera toxin B and horseradish peroxidase crystals by Morinaga et al. In Morinaga et al.'s experiment, the two markers were injected into the anterior L5–L6 intervertebral discs of rats followed by histological examination of the dorsal root ganglia. Surprisingly, labeled neurons appeared to be restricted to the L1–L2 level.

On this basis *it was hypothesized that the nociceptive fibers passed through the sympathetic trunk from L5–L6 to L1–L2, an inference later supported by Sekiguchi et al.'s demonstration of increased pain threshold following sympathectomy. However, this did not help to explain the sinuvertebral nerve's role in discogenic pain, as it was widely accepted that sympathetic nerves directly from the sympathetic trunk only innervated the anterior anulus fibrosis.*

Similar experiment by Cavanaugh et al. on the posterior aspect of the anulus verified a clear nociceptive ascending track along sympathetic afferents from lower lumbar levels.
The sinuvertebral nerve also innervates a number of additional structures, one being the anterior portion of the dura mater within the spinal canal. Each sinuvertebral nerve sends a long descending meningeal branch that extends two seg- ments caudally and a shorter ascending branch that traverses as far as one rostral segment. The plexus formed by the anas- tomoses of these branches covers the ventral surface of the dura mater and extends to the lateral aspects, but never reaches the dorsal surface, which remains devoid of nerve supply. The three most rostral sinuvertebral nerves ascend through the foramen magnum, at which point they innervate the dura mater covering the clivus within the posterior cranial fossa.

The sympathetic fibers carried in the sinuvertebral nerve are thought to innervate much of the surrounding vasculature, including the vessels that supply blood to the outer anulus, end plates, vertebral bodies, and marrow. It has been speculated that these fibers are primarily involved in vasomotor regulation, although some have been found to travel distal to the blood vessel, suggesting an additional undetermined function.
Finally, sinuvertebral nerves have also been found to terminate in the periosteum of the vertebrae as well as the liga- ments of the zygapophyseal and median atlanto-axial joints. The sinuvertebral nerve does not supply sensation to the facet joint, another common source of chronic back pain said to be mediated primarily by the medial branch of the posterior ramus

DISCOGENIC PAIN AND S.V.N.

Although the sinuvertebral nerve fibers are said to terminate in the outer anulus, it is now widely accepted that this end point is not permanent. **Studies of healthy patients normally show neural penetration of the anulus at about 3 mm, corresponding to the three outer lamellae. However, degenerative discs have shown penetration of nerve fibers as far as the inner one third in one study, and into the nucleus pulposus in another**. Earlier studies focused on the findings of the herniated nucleus pulposus and the sinuvertebral nerve fibers. Various studies have demonstrated that upon contact with the nucleus pulposus, nerve fibers showed reduced spinal nerve root conduction velocities, induced nerve degeneration, increased nerve discharge, increased intraneural capillary permeability, and attraction of inflammatory cells.

Provocative discography is still the gold standard for diagnosing discogenic pain.

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ORIGINAL ARTICLE

Clinical anatomy of the lumbar sinuvertebral nerve with regard to discogenic low back pain and review of literature

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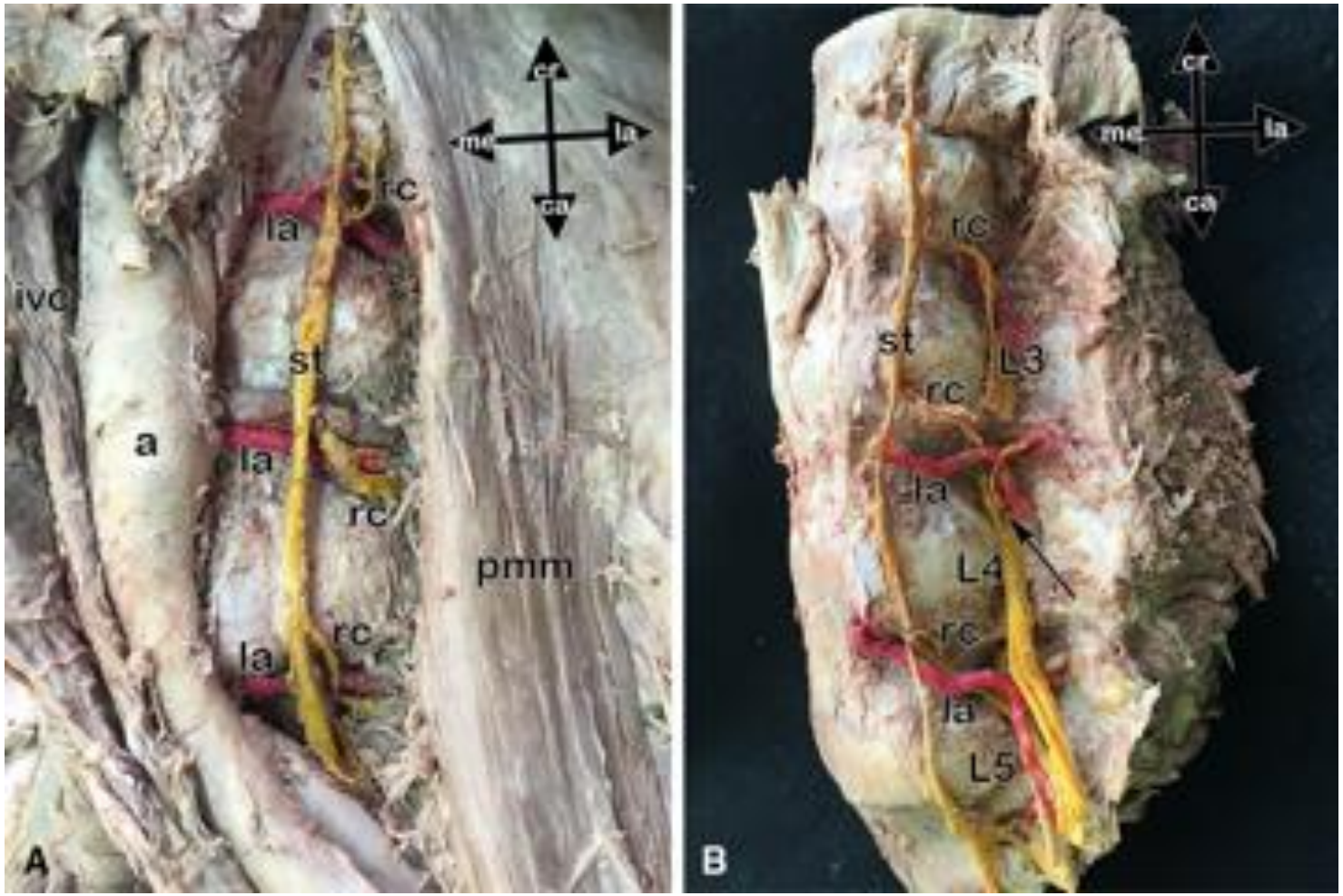
Six spine blocks (including vertebral bodies L3–S1), corresponding to six embalmed human body-donors belonging to the Body Donation Center and Dissection Rooms, Complutense University of Madrid, dissected (three female and three male between 59 and 94 years of age).



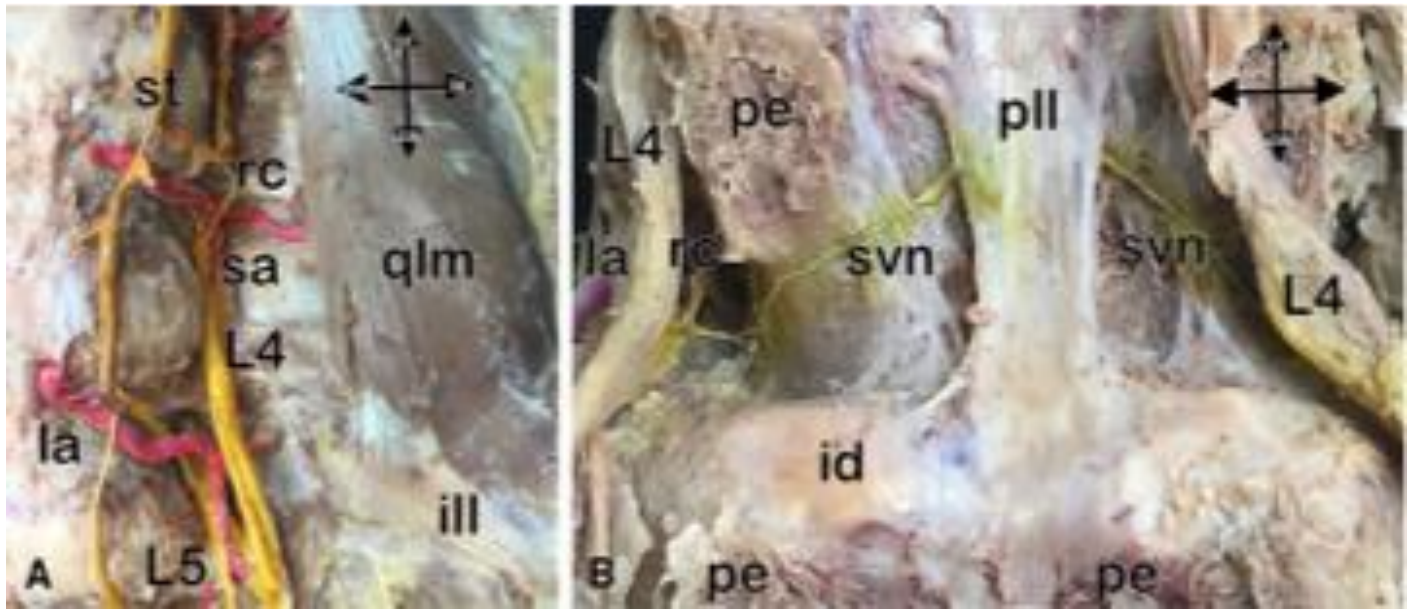
a. First step in the left lateral approach to the lumbar spine: Identification of the sympathetic trunk (st) and rami communicantes (rc), betWeen the psoas major muscle (pmm) and aorta (a) With lumbar arteries (la) and inferior vena cava (ivc).
b. Second step in the lateral approach; after removing the psoas major muscle and the aorta have been removed, the connection of the rami communicantes (rc) With the ventral branches of the lumbar nerves (L3, L4, L5) can be observed. The black arroW shoWs the level of the sympathetic origin of the sinuvertebral nerve. cr: cranial, me: medial, la: lateral; ca: caudal

The origin, course and distribution of the SVN have been discussed recently but they are still not consistent in the literature. Most authors define the origin as a neural branch emerging from the spinal nerve and a sympathetic postganglionic branch developing from the rami communicantes.

In contrast, several studies define a single origin either as a spinal or a sympathetic branch.

Different patterns of its course have been proposed: an ascending course, a descending course, a horizontal oblique course and a mixed course including an ascending and descending branch.

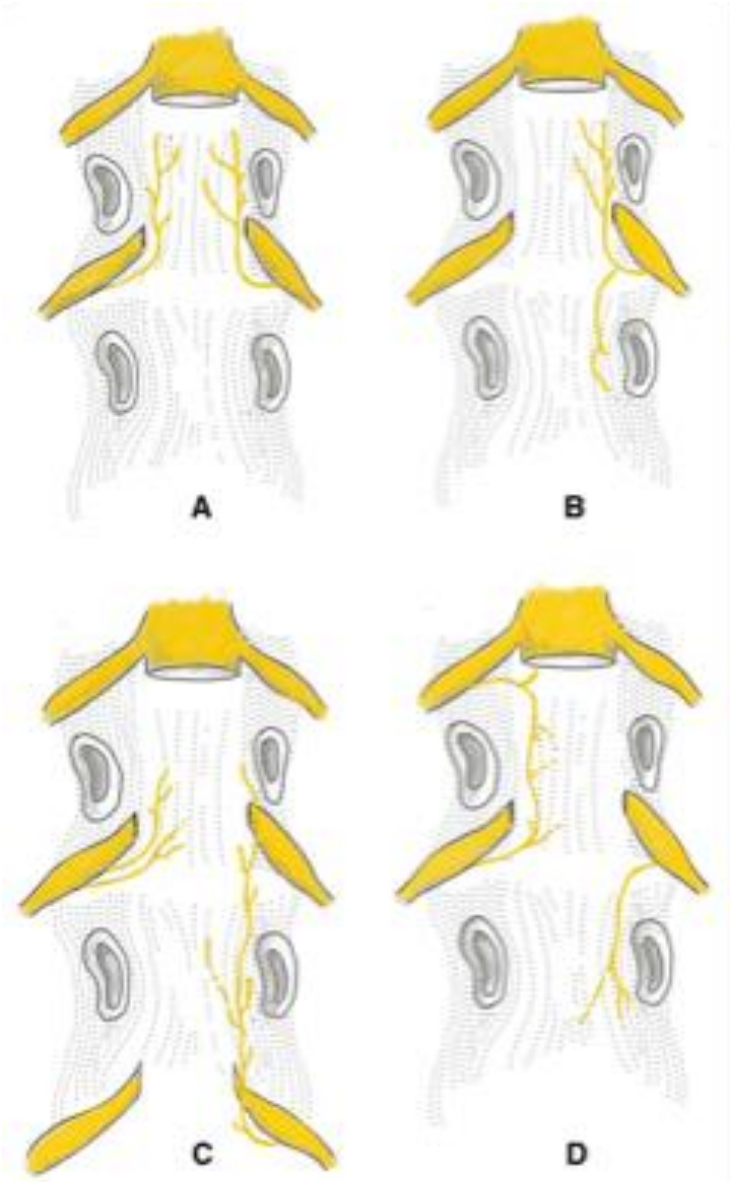
A plexiform pattern has also been described



Origin of the sinuvertebral nerve (SVN):

a. View of the origin of the sympathetic root (arrow) arising from the ramus communicans (rc) of the sympathetic trunk (st) in the encircled area corresponding to the connection of the ramus communicantes with L4 and the origin of the sinuvertebral nerve (arrow) entering into the vertebral canal with the spinal artery (sa) branch of the lumbar artery (la), iliolumbar ligament (ill) and quadratus lumborum muscle (qlm).
b. Posterior view of the lumbar spine after sectioning the vertebral pedicles (pe) and removing the vertebral arches. The intervertebral disc of the L4 segment (id) and posterior longitudinal ligament (pll) can be observed. The spinal and sympathetic roots (from L4 and ramus communicans (rc) make up the sinuvertebral nerve (svn). Cr: cranial, me: medial, la: lateral, ca: caudal

The origin of the SVN was always formed by two roots: a somatic root arising from the spinal nerve and a sympathetic branch from the rami communicantes (Fig. 3).
In 4 /48 intervertebral canals (8.3%), we found two SVN at the same level (Fig. 4a). In 35/48 intervertebral canals (72.9%), we found just one recognizable SVN (Fig. 4a). In 9/48 (18.75%), we found no SVN.
After the two branches united, the nerve entered the intervertebral canal near the inferior vertebral notch in a recurrent course (Figs. 3 and 4).
In 31 cases (72%), the SVN followed an ascending course that ended in the middle of the vertebral body covered by the posterior longitudinal ligament (Figs. 2c, 3, 4) (Table 2). In 10/43 SVN (23.3%), the nerve split into ascending and descending branches of equal length which ended at the
midline (Fig. 4b). In 1/43 SVN (2.3%), the ascending branch ended two levels cranially. A descending course of the SVN ending in the inferior disc was observed in 1/43 cases (2.3%) (Figs. 5 and 6).
In every case, these nerves supplied the dura mater, the posterior longitudinal ligament, blood vessels of the epi- dural space, the annuli fibrosi, the vertebral bodies and the superior or inferior intervertebral disc, depending on the course. The SVN was closely related to the spinal artery (Fig. 4a) and surrounded by the anterior vertebral venous plexus (Fig. 4b).
We have found that the SVN connected ipsilaterally in 12/43 cases (27.9%) (Figs. 6 and 7).



Our results suggest a general pattern of the SVN with two different roots, spinal and sympathetic, and an initial recurrent course entering into the vertebral canal, just close to the inferior vertebral notch of the pedicle.
The SVN can then follow different courses: an ascending course, a mixed course dividing into two branches (ascending and descending) or an exclu- sively descending course. These branches ended deep to the posterior longitudinal ligament after spreading among the adjacent structures. The terminal branches of the SVN had ipsilateral connections but they did not cross the midline; no contralateral connections were found.

A thorough understanding of the anatomy of the SVN might lead to significant benefits in therapy of discogenic low back pain. We suggest blocking the SVN at the level of the inferior vertebral notch of two adjacent segments.

ELSEVIER

The SPINE JOURNAL

The Spine Journal 22 (2022) 472–482

Basic Science

Origin, branching pattern, foraminal and intraspinal distribution of the human lumbar sinuvertebral nerves

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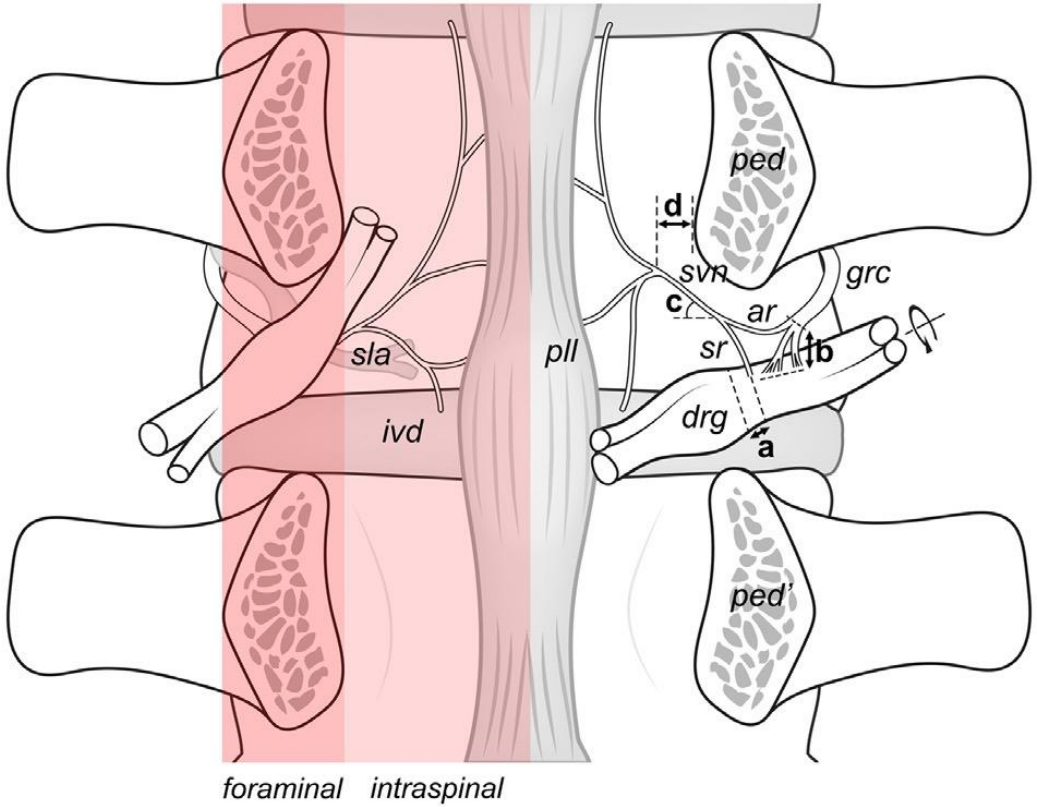
Murine studies indicate that **lower lumbar discogenic pain** is mediated by **two separate pain pathways**:

- **segmentally** via the somatic SVN root to its corresponding level DRG neurons,
- **nonsegmentally** via the autonomic SVN root, with nociceptive fibers ascending through gray rami communicantes and the sympathetic trunk to L1–L2 DRG neurons.

It is not known whether L5 LBP in humans is similarly transmitted nonsegmentally to L1–L2 DRGs. Remarkably, the murine model is used to justify several therapies, which presumably target the nonsegmental pathway, frequently with disappointing results.

Zhao et al. reported both origins, but their study does not indicate if a dual root lumbar origin co-exists, nor if the somatic and/or autonomic root contributions differ per lumbar level.
Precise knowledge of lumbar SVN origins is, however, crucial to unraveling discogenic LBP pathways and in treating it. We therefore studied the lumbar anatomy of the SVN and specifically focused on its somatic and/or autonomic origins at higher (L2) vs lower (L5) lumbar levels. Additionally, we provide a detailed description of its foraminal and intraspinal branching pattern and distribution at these lumbar levels.

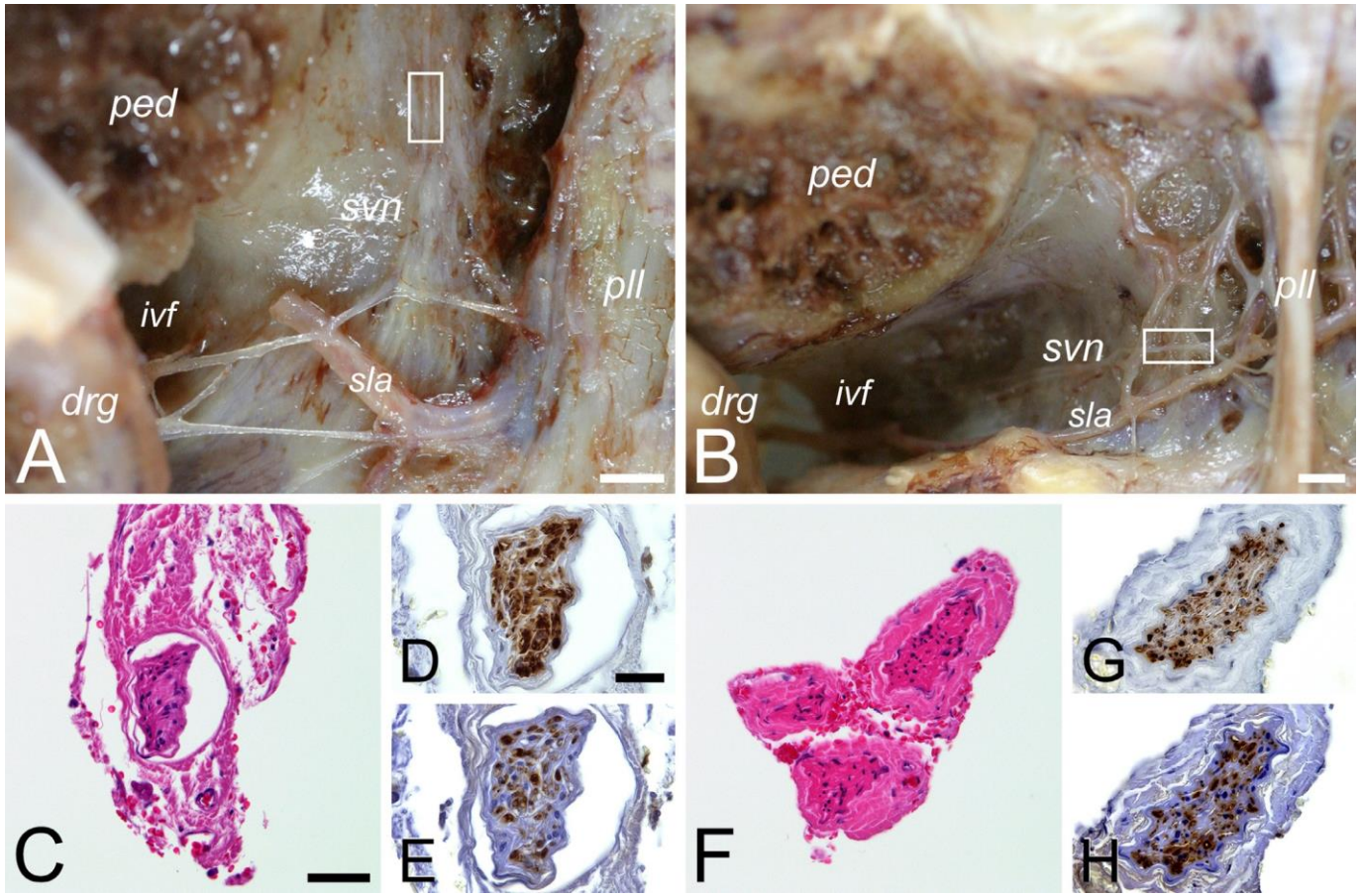


The sinuvertebral or recurrent meningeal nerve of Luschka (ramus meningeus nervi spinalis) is located bilaterally on every vertebral level, innervating:

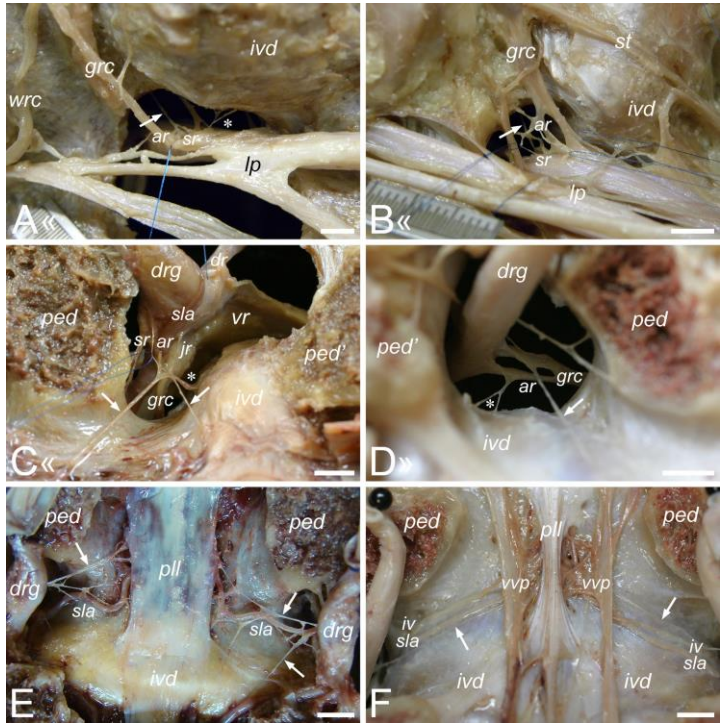
- the posterior intervertebral disc (IVD)
- posterior longitudinal ligament (PLL)
- vertebral body and pedicles, and associated soft tissues in the intervertebral foramen (IVF)
- anterior spinal canal.

In humans, the sinuvertebral nerve (SVN) has been described at cervical, thoracic, lumbar and sacral levels, but in greatest detail in the lumbar region.

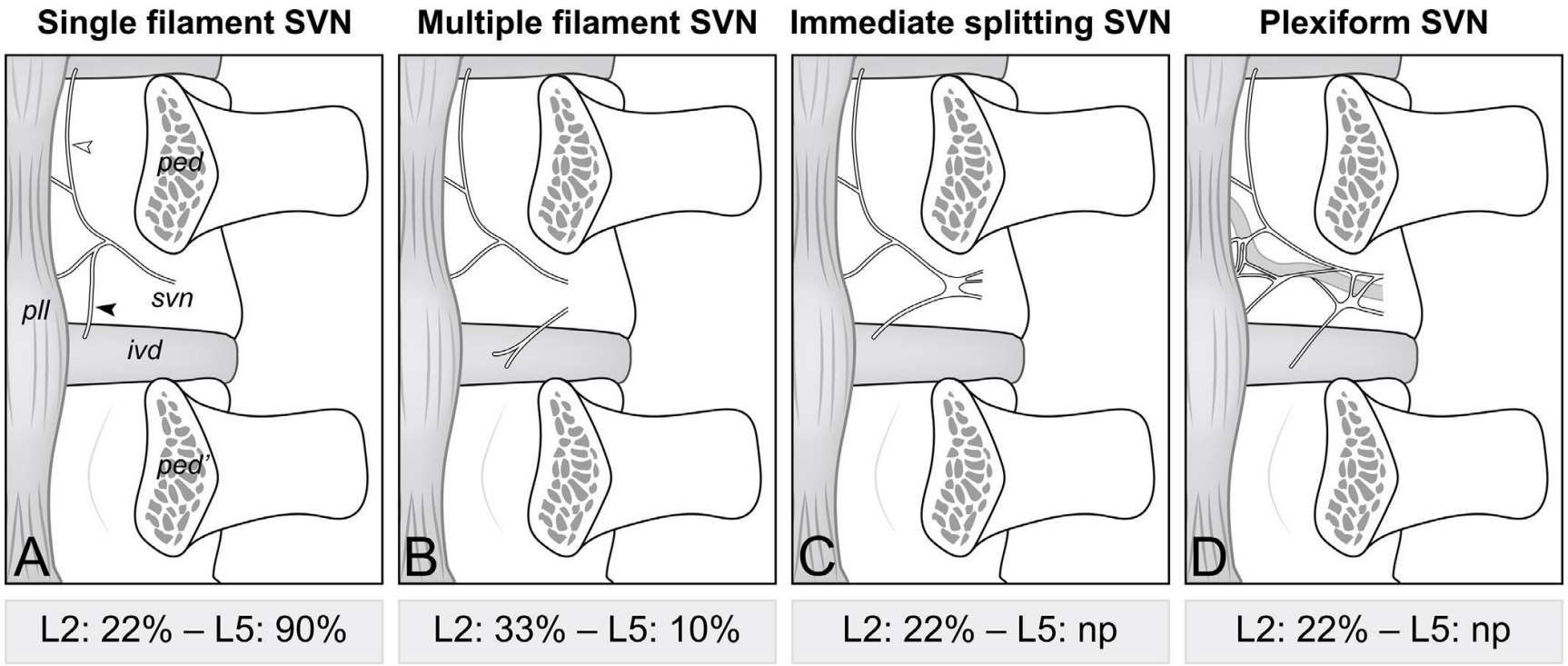
In the classic pattern, the SVN receives a somatic contribution from the spinal nerve or its ventral ramus and an autonomic contribution from the gray ramus communicans, which unite to form a single SVN proper that continues medially in the IVF. The SVN is located ventral to the dorsal root ganglion (DRG) in the ventral portion of the IVF, and generally travels alongside the spinal branch of the lumbar artery. Lateral to the PLL, the SVN splits into an ascending and a lesser descending branch, which may or may not have multisegmental ramifications and interconnect with sub- and superjacent SVNs.



Histological characterization of L2 and L5 sinuvertebral nerves. Tissue samples from microdissected sinuvertebral nerves (SVNs) were verified for nerve tissue using hematoxylin and eosin (HE) staining and immunostaining for neurofilament (neuronal marker) and S100 (Schwann cell marker) proteins. (A,B) Dorsal view of L2 (A) and L5 (B) SVNs in the anterior intervertebral foramen (IVF) and vertebral canal after removal of the posterior arches, zygapophyseal joints and spinal cord with dura, pedicle reduction, and retraction of the dorsal root ganglion (DRG). (A) Plexiform type SVN; ascending branch (left side). (B) Single filament type SVN; SVN proper (left side). (C–H) Tissue sections taken from the level indicated by the box in A (C–E) and B (F–H) and stained with HE (C,F), and for S100 protein (D,G) and neurofilament protein (E,H). drg, dorsal root ganglion (retracted laterally); ivf, intervertebral foramen; ped, pedicle; pll, posterior longitudinal ligament; svn, sinuvertebral nerve; sla, spinal branch of the lumbar artery. Scale bar: 2 mm (A and B); 50 mm (C and F); 25 mm (D,E,G and H)



Origin and course of the L2 and L5 sinuvertebral nerve. (A,B) Ventrolateral, (C,D) dorsolateral and (E,F) dorsal views of L2 (A,C,E) and L5 (B,D,F). (A) Dual (somatic and autonomic) L2 sinuvertebral nerve (SVN) origin. Ventrolateral view of the L2 intervertebral foramen (IVF) after resection of the psoas major muscle; the gray ramus communicans is retracted. Single filament type SVN (arrow) formed by two somatic roots and one autonomic root. (B) Dual (somatic and autonomic) L5 SVN origin, found in 40% of sides. Ventrolateral view of the L5 IVF after resection of the psoas major muscle; outer somatic SVN roots pulled apart and gray ramus communicans partly retracted. Single filament type SVN (arrow) formed by three somatic roots and one autonomic root. (C) Classic dual (somatic and autonomic) L2 SVN origin, found in 88.9% of sides. Dorsolateral view of the right L2 IVF from within the spinal canal with the dorsal root ganglion (DRG) and somatic SVN root retracted with monofilament suture, and the spinal branch of the lumbar artery reflected onto the DRG. Immediate splitting type SVN (arrows). After root convergence into SVN proper, immediate splitting into an ascending and descending branch. Note additional junctional root emerging from the ramus communicans-spinal nerve junction. (D) Pure autonomic L5 SVN origin, found in 60% of sides. Dorsolat- eral view of the left L5 IVF from within the spinal canal with the DRG retracted. The autonomic root continues as a single filament type SVN (arrow). (E) Foraminal and intraspinal distribution of the L2 SVN. Dorsal view of the L2−L3 anterior epidural space. Immediate splitting (left side) and plexiform (right side) type SVNs (arrows). The SVN courses in the superior or middle anterior portion of the IVF, ramifies around the spinal branch of the lumbar artery and forms a plexus lateral to the posterior longitudinal ligament (PLL), innervating both the PLL and sub-/superjacent intervertebral discs (IVDs). (F) Foraminal and intraspinal distribution of the L5 SVN. Dorsal view of the L5−S1 anterior epidural space. Single filament type SVNs (left and right side; arrows). Bilat- eral intraspinal branching points, located deep to the anterior internal vertebral venous plexus. Asterisk in A, C and D indicates IVD nerve branches from ventral ramus of spinal nerve, SVN, and gray ramus communicans, respectively. ar, autonomic SVN root; dr, dorsal ramus of spinal nerve; drg, dorsal root ganglion (retracted laterally); grc, gray ramus communicans; iv, intervertebral vein; ivd, intervertebral disc; jr, junctional SVN root; lp, lumbar plexus; ped, pedicle; ped', subjacent pedicle; pll, posterior longitudinal ligament; sr, somatic SVN root; sla, spinal branch of the lumbar artery; st, sympathetic trunk; vr, ventral ramus of spinal nerve; vvp, anterior internal vertebral venous plexus; wrc, white ramus communicans. Double sideways chevrons indicate cranial direction. Scale bar=5 mm.



Foraminal sinuvertebral nerve types and frequencies (%) at L2 and L5. Dorsal view of anterior vertebral canal after removal of posterior arches, zyga- pophyseal joints and spinal cord with dura, and removal of the spinal roots-dorsal root ganglion-spinal nerve complex. Four distinct foraminal sinuvertebral nerve (SVN) types are recognized: (A) single filament, (B) multiple filament (parallel or diverging), (C) immediate splitting, and (D) plexiform types. At L2, all four SVN types (A–D) are found, whereas at L5 only single (A) or multiple filament (B) type SVNs are present. Note that the descending SVN branch (closed arrowhead) innervates the corresponding (L2/3 or L5/S1) intervertebral disc (IVD), whereas the ascending branch (open arrowhead) innervates the superjacent IVD. ivd, intervertebral disc; ped, pedicle; ped', subjacent pedicle; pll, posterior longitudinal ligament; svn, sinuvertebral nerve.

DISCUSSION

In the present study, we examined the anatomy of the SVN at high (L2) and low (L5) lumbar levels, with special focus on its somatic and autonomic origins. This knowledge is important for unraveling the 'wiring diagram' of discogenic LBP, and hence, to improve targeting of treatment modalities. Furthermore, it may contribute to preventing iatrogenic damage to the SVN during (transforaminal) surgical approaches to the lumbar spine. Our data show that a dual root origin is common at L2 and that at L5 there is autonomic root predominance but not exclusivity. The finding that about half of L5 SVNs are formed by a dual root origin suggests that lower lumbar discogenic pain may not only be transmitted by nonsegmental neural pathways as is widely accepted in clinical practice, but also segmentally.

Origin of the SVN

In our study, nearly 90% of SVNs at L2 arose from both somatic and autonomic roots, confirming findings of most authors. At L5, our results confirm an autonomic root predominance, but not exclusivity, as 40% of L5 SVNs contained an additional somatic component. Macroscopically, the SVN at L5 is thus not always purely autonomic as previously reported

While individual root identification is difficult, we have clearly demonstrated somatic contributions to the SVN from the ventral ramus, spinal nerve and DRG both at L2 and L5

SVN DISTRIBUTION IN THE SPINAL CANAL

The present findings that the intraspinal SVN distribution does not differ at L2 and L5 and that the SVN does not extend beyond its level of origin are in accordance with Luschka's original description, Lazorthes et al., and Bogduk et al.. Although branching of the SVN into ascending, descending and transverse branches has been described, its precise branching point has not been further detailed. Branching occurred intraspinal in the subarticular or central canal zone, and generally more medially at L5 than L2, irrespective of SVN type.

The posterior L2/3 and L5/S1 IVDs were innervated ipsilaterally by the descending branch of the parent SVN and ascending branch of the subjacent SVN, that is by two spinal levels.
This is in accordance with Lazorthes et al. and Bogduk et al., but in contrast to Groen et al., who found that lumbar posterior IVDs were innervated by the parent, sub- and superjacent SVNs, that is by three levels.

Descending SVN branches passing between the lateral PLL extension and IVD were not traced further, but descending SVN branches from superjacent levels were not found at L2 and L5, neither free lying nor appearing from between the superjacent lateral extension of the PLL and its associated IVD.

CLINICAL IMPLICATION

Our results indicate that 60% of L5 SVNs are formed purely by autonomic roots. In the absence of a somatic root contribution, discogenic pain transmission can occur via the subjacent SVN, as an IVD is innervated by two spinal levels (this study). Alternatively, it might be mediated non- segmentally through the previously described autonomic inflow diversions, whereby nociceptive fibers from lower lumbar IVDs ascend via the autonomic SVN root through gray rami communicantes and the sympathetic trunk to L1–L2 DRG neurons. So far, however, this neural pathway has only been described in rats and awaits further human study.

Remarkably, current therapies for discogenic LBP specifically aim to target this nonsegmental pathway by interrupting pain transmission through nerve blocks, transection, or radiofrequency lesioning of the L2 DRG, spinal nerve or ramus communicans. These interventions are not always effective. Since we have found that 40% of SVNs at L5 are formed also by somatic roots, which are presumed to contain segmental nociceptive fibers, interruption of the nonsegmental pathway alone is expected to provide only partial pain reduction and may explain some of the disappointing results in the aforementioned studies. Interindividual "wiring diagram" variations may thus call for different therapeutic approaches to pain reduction in patients with discogenic LBP.

Although the precise role of the SVN in discogenic LBP has not been fully established yet, data from immunohisto-chemical studies have clearly revealed that healthy and painful lumbar posterior IVDs are innervated by nociceptive fibers from the SVN, indicating a function in pain perception. Whether these nociceptive fibers indeed mediate painful stimuli both segmentally and nonsegmentally awaits further (functional) studies.

CONCLUSION

At L2, the SVN arises in nearly 90% of sides from both somatic and autonomic roots and at L5 in 40% of sides.
The remaining SVNs are formed by purely autonomic roots.

Lower lumbar discogenic pain is presumably mediated segmentally via the somatic SVN root and nonsegmentally through the autonomic SVN root; targeting only the non- segmental pathway may provide incomplete pain reduction.

In the IVF, the L2 SVN generally consists of numerous filaments, whereas at L5 90% contains a single SVN filament. Relating SVN anatomy to microsurgical spinal approaches may prevent iatrogenic damage to the SVN and the formation of postsurgical back pain.

DURA MATER

Anatomic and Biomechanical Properties of Human Lumbar Dura Mater

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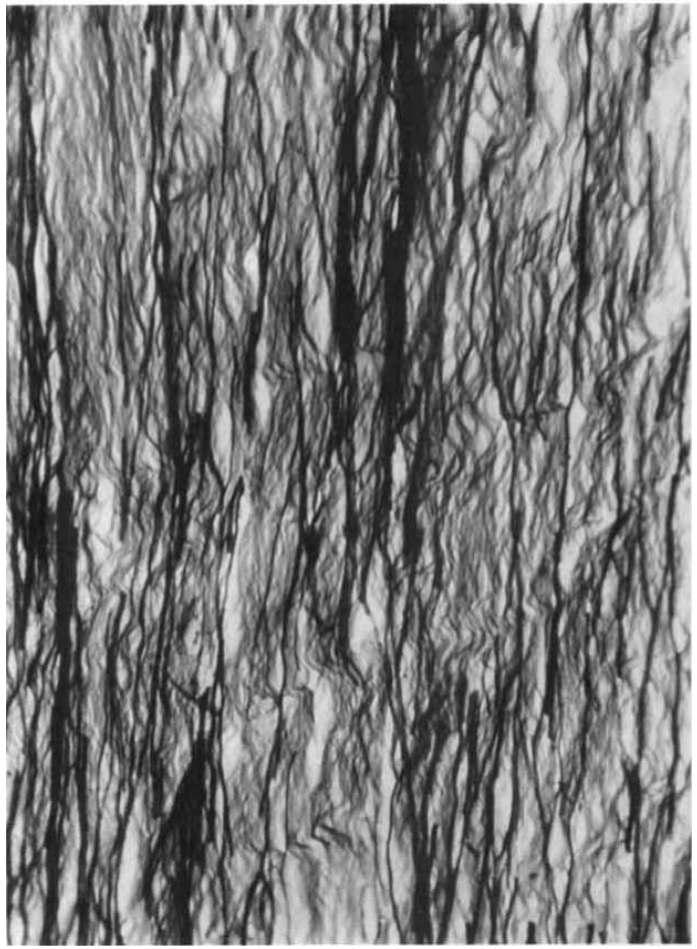
Departments of Anesthesiology and Biomedical Engineering, University of Miami/Jackson Memorial Medical Center, Miami, Florida

1993

Specimens of human dorsal lumbar dura mater were obtained at autopsy from nine subjects ranging in age from 15days to **81** yr and were placed in normal saline and kept refrigerated until examination.



Human dorsal lumbar dura. x 200.

This study confirms that human lumbar dura mater is a longitudinally oriented structure as originally described by Greene in 1926 (5) and by modern anesthesia texts.

Biomechanical testing, which showed greater tensile strength and stiffness in the longitudinal direction, is consistent with this structural arrangement. Relaxation, a property of a viscoelastic material, was demonstrated by the dura's tendency to return to a less energetic state when tissue distraction was halted. The dura exhibited neither pure elastic nor pure viscous behavior, but a combination of properties reflecting its relatively elastic collagen and elastin fibers being contained in a viscous intercellular ground substance.

Clinically,the dura is lessresistant to transverse stresses than to longitudinal stresses;up to 78%of lumbar vertebral impaction fractures in one study were as- sociated with longitudinal dural lacerations.The postulated lateral traction on root sleeves combined with an inherently weaker dura in the transverse direction readily explains these findings.

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Ultrastructure of the human spinal arachnoid mater and dura mater

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Surgical specimens from the mediodorsal portion of normalspinalmeningeswereobtainedfrom5patients (2 men, 3 women, aged 7-45 y) undergoing neuro- surgeryatthethoracolumbarandlumbosacralspinal levels.

Human spinal dura and arachnoid, obtained during neurosurgical operations, were studied by transmission electron microscopy. The ultrastructure of spinal meninges largely conformed to the morphology of the cranial meninges, but some minor differences were detected.

The dura was composed of an outermost loosely arranged fibroelastic layer, a middle basically fibrous portion and an innermost cellular layer (dural bordercellayer).The dural border cell layer was characterised by multiple interdigitating cel processes, no extra cellular collagen, significant extracellular spaces and few cel junctions. Paravascular vesiculated nerve profiles were encountered within the fibroadipose epidural tissue. The arachnoid was composed fan outermost portion (arachnoid barrier cel layer), presenting tightly packed cels, numerous tight junctions and no extracellular collagen. In view of its numerous tight junctions, the arachnoid barrier cel layer is considered to represent an effective morphological and physiological meningeal barrier between the cerebrospinal fluid in the subarachnoid space and the blood circulation in the dura. The arachnoid barrier layer was always characterised by a distinct continuous basal lamina on its inner surface towards the innermost collagenous portion ofthe arachnoid (arachnoid reticularcellayer). The interweaving arachnoid trabecular cels within this layer possessed numerous mitochondria and were anchored to the inner surface ofthearachnoidbarriercellayerbydesmosomes.An additionallayerofflattenedbranchingcelswas demonstrated along the inner surface of the arachnoid reticular cel layer and assumed tobe an 'arachnoid bordercel layer'. Morphological data suggest that the dura and arachnoid closely adhere at spinal levels in man with out any naturally occurring' subdural space'. However,structurally, the dural border cel layer forms a weak cel layerat the dura-arachnoid continuum that is easily disrupted. The creation of an artifactual subdural space at spinal levels is discussed.

The spinal meninges form a tubular sheath around the spinal cord, anchored on each side to the dura by the dentate ligaments (Nicholas& Weller,1988).
The dura is known to be displaced during flexion and extension movements of the spine (Lang, 1983; Tencer et al. 1985). Furthermore, it is tensed during limb movement as a result of the displacement of the spinal nerves and their dural cones in the intervertebral foramina (Sunderland,1980). On morphological grounds, the presence of numerous elastic fibres within the fibrous dura implicates functionally considerable flexibility and elasticity when subjected to stretching and deforming forces during movements and postural changes.

We found in frequent para vascular vesiculated nerve profiles with in the epidural fibroadipose tissue. These nerve endings are probably sensory in function. However, on morphological grounds the functional interpretation of vesiculated nerve profiles is uncertain (Vandenabeeleetal.1995).

No neural structures could be identified in 'the present material of spinal dura. Indeed, recent histochemical studies demonstrated that the dorsal spinal dura does not have a rich
Innervation in contrast to the cranialdura (Groenet al.1988;Kumaretal.1996). Groen et al.(1988) suggested that the paucity of dorsal dural nerves correlates with clinical reports of the painlessness of dural puncture (Cyriax,1978;Wyke,1980). Fur- thermore, the specimens studied by E Maresmalland came from circumscribed regions of the dorsal dura. According to Kumar et al.(1996), th espinal dura serves primarily as a protective membrane enclosing the spinal cord and cerebrospinal fluid. They suggested that the spinal dura plays a limited role in the pathogenesis of pain, in contrast to the cranial dura which is known to be richly innervated.

ELSEVIER

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THE SPINE JOURNAL

Basic Science

Analysis of dural sac thickness in human spine—cadaver study with confocal infrared laser microscope

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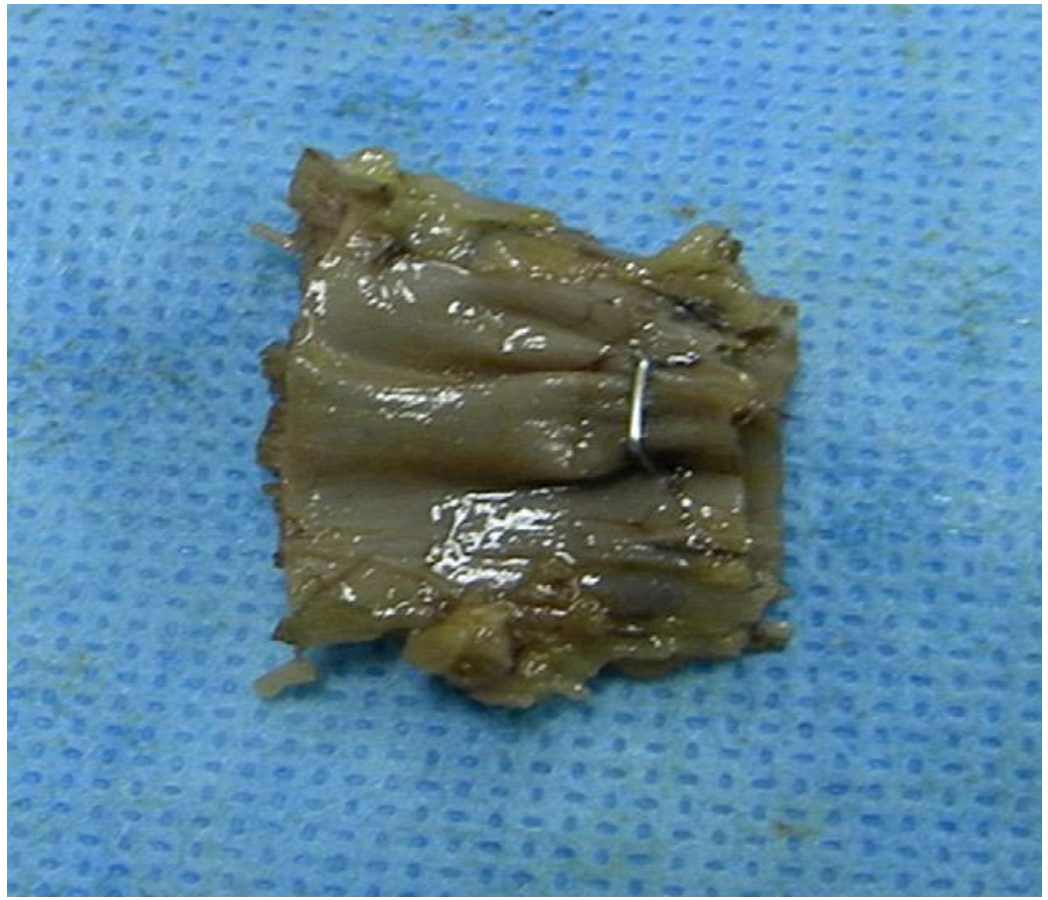
19 human cadavers with no prior history of spinal surgery or deformity. Seventeen specimens from T1/T2 to L5/S1 were obtained from each of 19 cadavers, a total of 323 specimens.



Overall mean dural sac thickness was 0.30760.122 mm in this human cadaver series.
Dura thicknesses differed significantly at different levels (p5.046). Overall, dural thickness was highest at T9/T10 and lowest at L2/L3 (p5.0007) as well as highest at the lower thoracic level followed by the upper thoracic and lumbar levels (p5.003).
In addition, dural sac thickness was found to increase slightly but significantly with age (p5.019). However, dural thickness was similar between men and women (p5.123). And, no significant dural thickness differences were found for stenotic and nonstenotic lesions (p5.885).

CONCLUSION: Dural sac thickness was found to be significantly dependent on spinal level and age in human cadavers.
An appreciation of dural sac thickness differences can be useful in the clinical field, and it is hoped that this encourages further study of dural physiology

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Research Article

Neural-Dural Transition at the Thoracic and Lumbar Spinal Nerve Roots: A Histological Study of Human Late-Stage Fetuses

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We examined semiserial paraffin sections (0.5 mm interval, 10 μm thickness) of the vertebral columns from 12 human fetuses (28–30 weeks; crown-rump length (CRL), 230–260 mm).

These specimens included 18-19 pairs of spinal nerve roots and dorsal root ganglia that were from the first thoracic to the first or second sacral levels as well as the most proximal part of all 12 ribs

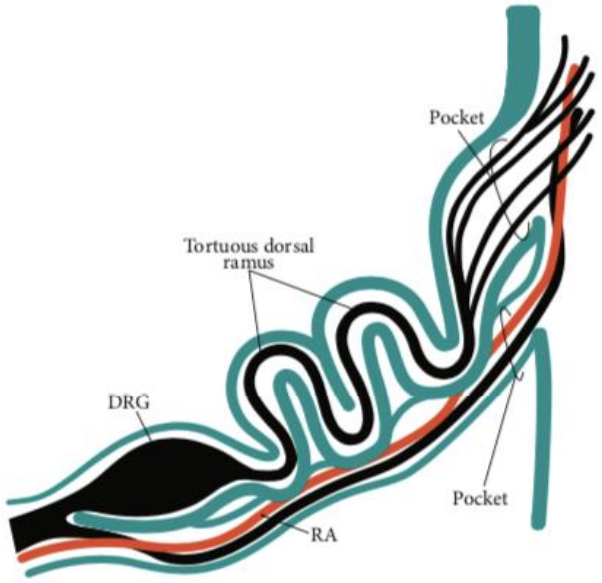

FIGURE 7: A diagram showing a tortuous course of the dorsal ramus starting from a large pocket-like protrusion of the dura. Note a difference in thickness of the dural sheath (blue) between the dorsal root ganglion (DRG) and the nerve rootlets from the spinal cord. In this diagram, the ventral ramus also accompanies a small pocket but it takes a straight course with the anterior radicular artery (red, RA).

Epidural blocks have been used extensively in infants. However, little histological information is available on the immature neural-dural transition.

The neural-dural transition was histologically investigated in 12 late-stage (28–30 weeks) fetuses.

The dural sheath of the spinal cord was observed to always continue along the nerve roots with varying thicknesses between specimens and segments, while the dorsal root ganglion sheath was usually very thin or unclear. Immature neural-dural transitions were associated with effective anesthesia. The posterior radicular artery was near the dorsal root ganglion and/or embedded in the nerve root, whereas the anterior radicular artery was separated from the nearest nerve root. The anterior radicular artery was not associated with the dural sheath but with thin mesenchymal tissue. The numbers of radicular arteries tended to become smaller in larger specimens. Likewise, larger specimens of the upper thoracic and lower lumbar segments did not show the artery. Therefore, elimination of the radicular arteries to form a single artery of Adamkiewicz was occurring in late-stage fetuses.

The epidural space was filled with veins, and the loose tissue space extended ventrolaterally to the subpleural tissue between the ribs.

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Spinal dura mater: biophysical characteristics relevant to medical device development

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GROSS ANATOMICAL PROPERTIES

Although dura mater is a continuous membrane that encloses the brain and the spinal cord, **the spinal dura mater differs from the cranial dura mater**. The external endosteal layer of cranial dura mater ends at the foramen magnum continues as the periosteum of the spinal canal. Thus, **the spinal dura mater is composed of the inner or meningeal layer of cranial dura mater**. Caudally, the spinal dura ends at the level of S2 where it becomes a thin cord- like extension (coccygeal ligament or filum terminale) that anchors the dural sac to the sacral periosteum. *The dura mater is attached to the circumference of the foramen magnum and the second and third vertebrae. It is also attached anteriorly to the posterior longitudinal ligament by the fibrous Bands of Hofmann. The posterior surface is relatively more mobile and the connective tissue (the meningovertebral ligaments) is less fibrous*. Thus, the anterior attachment supports and secures the dura anteriorly in the spinal canal while the posterior surface is allowed greater mobility.

The dural membrane serves not only as a sheath for the spinal cord but also localises and suspends it though the denticulate ligaments that are located between the successive nerve roots. There are also other ligaments and trabeculations in the subdural space that provide additional stability to the spinal cord inside the dural sac. The most notable of these is the fibrous septum posticum which is more fully developed in the upper thoracic spine. The dimensions and morphology of the intrathecal space are different from those of the spinal cord, and vary along the length of the spine.

The arterial irrigation of the spinal dura mater comes from the ventral (intraspinal) division of each dorsal spinal artery, with bilateral segmental distribution. In the upper segment, there is anastomosis between the dorsal meningeal arteries and the dural branches of the vertebral, occipital and ascending pharyngeal arteries. The venous drainage is by the extradural venous plexus, with functional valves in the veins at the radicular levels to prevent retrograde flow into the intrathecal extrinsic venous system of the spinal cord. **Groen et al. studied the dural innervation and concluded that the dorsal dura has much smaller innervation compared to ventral dura, since the nerves do not reach the medial region in the dorsal side. They further noted that the dorsal nerves are derived from ventral dural plexus, which receives contributions from sinuvertebral nerves, and from the nerve plexus of the posterior longitudinal ligament and the radicular branches of radicular arteries.**

COMPOSITIONAL TISSUE AND MICROSCOPIC PROPERTIES

Dura mater is composed largely of fibroblasts, collagen and elastic fibres embedded in an amorphous extracellular ground substance. **The collagen provides tensile strength while the elastic fibres provides flexibility and elasticity**. The dura has been described as a viscoelastic biological material under normal physiological strains. Although there is some controversy, **the collagen fibres are mostly longitudinally oriented**. Therefore, the greater tensile strength and stiffness are in the longitudinal direction. Under the microscope, tightly packed collagen fibres are intermixed with elastin fibres.

Vandenabeele reported three distinct layers. First, there was a thin outermost portion with a thickness of 2 mm, with a low density of collagen and elastin fibres and sinuous parallel cell processes, forming a boundary with the epidural space. Second, the middle and thicker portion was richly vascularised and abundant in extracellular collagen intermingled with microfibrils, elastin fibres and some fibroblasts. Lastly, the inner layer, in intimate contact with the parietal arachnoid, presented dark cells ~8 μm thick, with interdigitated cell extensions, enlarged extracellular space, and an absence of a collagen reinforcement— the so-called "dural border cell layer". The latter demonstrated continuity between the dura and arachnoid layer.

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Dura Mater: Anatomy and Clinical Implication

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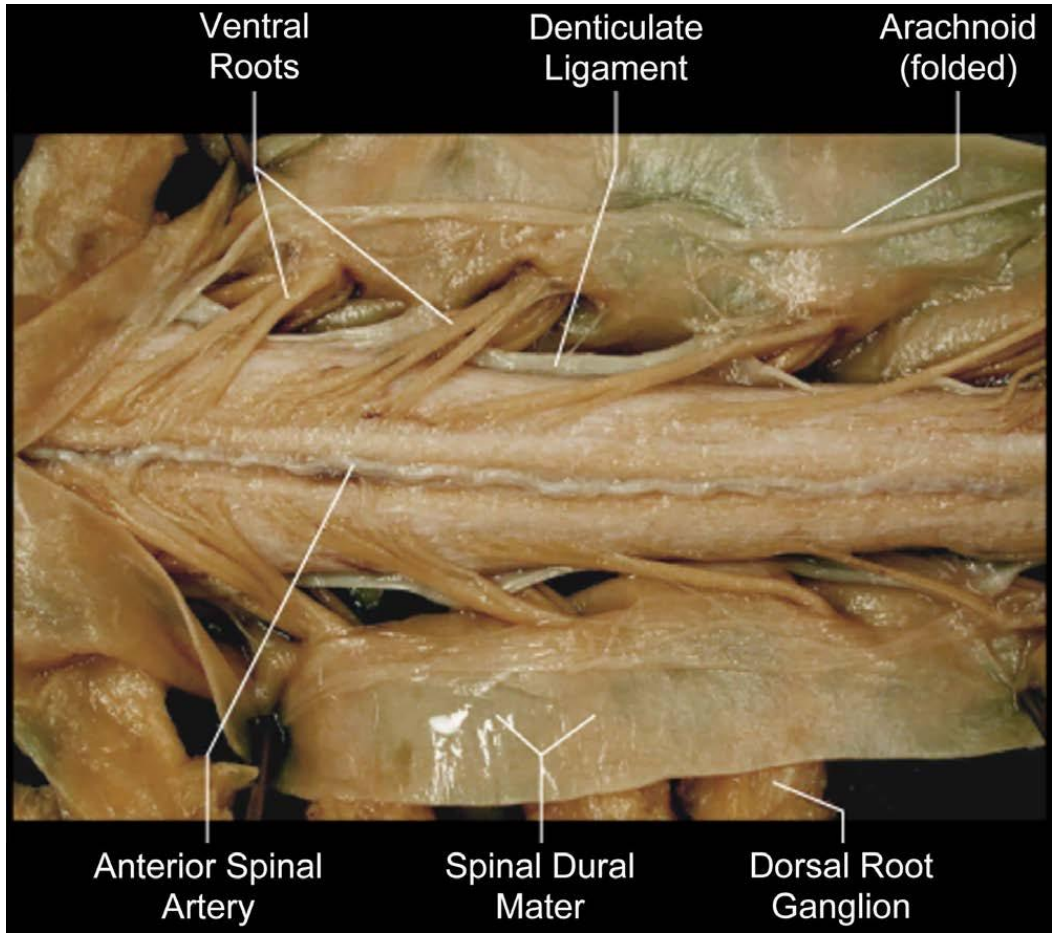

The spinal dura mater (SDM) is an inelastic collagen fiber tube that forms a loose sheath around the spinal medulla and closely matches the vertebral canal curvature. CSF, which relies on hydrostatic, respiratory, and pulsating influences, keeps the dura under stress. The dura stretches from the occipital bone foramen magnum to the sacral canal and is invested with the spinal cord filum terminale at S3 level, which blends with the coccyx periosteum. A potential cavity, the subdural area, separates the spinal dura mater from the arachnoid mater. However, both membranes are usually in close contact with each other, except where a minute quantity of CSF separates them. The dura mater is divided into three layers: an outer fibroelastic layer of flattened cells with thin and long cell extensions toward the epidural space; a middle fibrous layer; and an inside boundary cell layer with extracellular spaces, few cell junctions, and no extracellular collagen. **There are several elastic fibers inside the dura, suggesting significant versatility and elasticity during motion and postural changes.**

Connections with Muscles and Ligaments

The ligamentum craniale durae matris spinalis (CDMS ligament) was originally described by Von Lanz as fibrous strands extending from the dura mater to the occipital bone, the posterior longitudinal ligament and the transverse atlas ligament. Subsequently, the CDMS attaches the atlas arch and axis, the occipital squama periosteum, and laterally the atlanto-occipital and atlantoaxial joints. More fibers originating from the flaval ligaments between C1 - C2 and C2 - C3 have been identified and other dura-connected fibers have been found between the C2 and C3 arches. Rutten and colleagues believe that during movement por- tions of the CDMS ligament act as a tensioner of the upper cervical vertebral column.

The SDM is also bound by connective tissue bands to the posterior atlanto-occipital (PAO) membrane at the atlanto-occipital joint, which generates a network and is where the rectus capitis posterior minor (RCPmi) is also detectable. The myodural relation between the RCPmi and the SDM can prevent the folding of the SDM towards the spinal canal, which tends to occur during neck and head extension. The obliquus capitis inferior (OCI) is connected to the posterolateral part of the dura mater and the rectus capitis posterior majör (RCPma) spreads through the atlantoaxial interspace to the posterior dura mater.

The **myodural bridge** between the SDM and the suboccipital muscles has significant clinical importance in that severe stresses can be transmitted to the dura across the myodural bridge, which is expressed as cervicogenic headache.

Attachments have been found between the posterior SDM and the nuchal ligament at the first and second vertebrae stages, which is important in head rotational movements.

A connection between the flaval ligament and the SDM was found at the level of the vertebral bodies in the upper and lower cervical spines. Other direct attachments at the level of C7/T1 were also described. The rear SDM is anchored through the posterior cervical epidural ligaments to the flaval ligament. Anterior displacement of the dura is indicated in the absence or malfunction of certain ligaments, which may contribute to flexion myelopathy.

Trolard's ligaments are also called the ventromedian ligaments associated with the posterior longitudin- al ligament (PLL). These are found in the lower lumbar and sacral spine, between the dura and the vertebral bodies and arc. The trousseaux fibreux of Soulié consists of a network of strong bundles which support the anterior epidural venous plexus and link the dura mater with the posterior longitudinal ligament and the periosteum.

Denticulate ligaments are fibrous structures that extend the entire length of each side of the spinal cord, separating the ventral from the spinal nerve dorsal roots. The toothlike processes of these ligaments are attached to the dura mater.

Extension and flexion of the spine is transmitted via the denticulate ligaments by the SDM to the pia mater, with the greater part of the forces being transmitted directly to the spinal cord via cranial and caudal attachments of the dura. The rhomboid halter is a thin, diamond-shaped connective tissue plate that is attached to the dura mater via the upper toothlike processes of the denticulate ligaments. It has been proposed that the rhomboid halter holds the cranial area of the spinal cord and the lower medulla oblongata segregated during neck flexion from the axis dens, the ligamentous apparatus, and the vertebral arteries. Forestier's opercula is situated at the level of each intervertebral foramen, which indicates a relation between the span of spinal nerve coverage and the periosteum of the individual vertebra.

Blood Supply

Vascularisation: The direction of the arteries of the spinal cord is very complex. Paired posterior spinal arteries and anterior spinal artery have SDM. Venous drainage occurs outside the vertebral column and the segmental veins through venous plexuses. Such valveless plexus veins have particular physiological signi- ficance. They can interact with the lumbar and intercostal veins, and with venous plexuses in the nuchal zone, which enables the venous blood to be drained multidirectionally without obstruction.

Innervation

The innervations are especially less dense dorsally than ventrally.
Dorsal dural nerves are derived from the ventral dural plexus, which is linked to the sinuvertebral nerves, the nerve plexus of the posterior longitudinal ligament, and the nerve plexus of segmental artery radicular branches.

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Focused Review

Innervation of the Anterior Spinal Canal: An Update

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Luschka was the first to describe the presence of a nerve re-entering the intervertebral foramen and terminating in the substance of the posterior longitudinal ligament and annulus fibrosus of the intervertebral disc.
This nerve became known as the recurrent nerve of Luschka, and today we refer to it, as the sinuvertebral nerve.

The sinuvertebral nerve entered the spinal canal through the intervertebral foramen by passing just inferior to the pedicle. Once in the canal, the nerve traveled superiorly along the edge of the posterior longitudinal ligament. During this course, multiple branches are given to the posterior longitudinal ligament. A multitude of smaller branches from the sinuvertebral nerve were identified descending from the intervertebral foramen to terminate at the intervertebral disc level of the parent ventral rami

The ascending and descending branches of the sinuvertebral nerve combine to form a plexus on the posterior longitudinal ligament. This plexus is most likely formed by anastamoses with branches from the sinuvertebral nerve on the opposite side and with those from superior and inferior adjacent levels (It is generally agreed that anastamoses do exist between ascending and descending branches of the sinuvertebral verve. The level of anastamoses still is in question, but prevailing data would suggest that it occurs one to two adjacent levels above and below its level of entry into the spinal canal)

Thick meningeal branches from the sinuvertebral nerve, thin branches from the nerve plexus of the dorsal posterior ligament, and small branches of perivascular nerve plexuses of the radicular rami of segmental arteries all coalesce to form an anterior nerve plexus on the ventral aspect of the dura mater.

Groen et al was able to demonstrate the presence of a dense plexus of nerve fibers on the ventral dura of the human fetus. A majority of these ventral fibers were thought to be autonomic in origin. Ahmed et al corroborated Groen's findings of autonomic fibers on the ventral dural surface.
More recent immunohistochemical studies have also demonstrated the presence of sensory afferent fibers lining the ventral dural plexus.

The nerve branches of the posterior ligament plexus also form the primary innervation of the posterior longitudinal ligament and postero-lateral aspect of the intervertebral disc.

Bogduk has also reported additional nervous innervation of the disc through pathways other than direct branches from the sinuvertebral nerve. These included direct branches from the ventral rami, and two types of branches from the rami communicantes. All of these branches enter the postero-lateral aspect of the intervertebral disc. Branches from the rami communicantes were also noted to travel caudally and overly the subjacent disc.

The advent of immunohistochemical techniques has led to reassessment of spinal neural elements.

For instance, a number of neuropeptides are known to occur in afferent nerve fibers.
These neuropeptides include:
substance P, somatostatin, cholecystokinin-like substance, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide(CGRP), gastrin-releasing peptide, dynorphin, enkaphalin, and galanin.

Substance P, vasoactive intestinal peptide, and calcitonin gene related peptide are believed to be specific sensory trans- mitters and may also be involved in nociceptive transmission, neurogenic inflammation, and skeletal metabolism.
By using specific antibodies to these peptides an afferent sensory fiber may be identified in spinal tissues, whereas primary motor fibers are not.

In 1995, Imai et al was able to demonstrate a dual innervation to the posterior longitudinal ligaments in rats.
A superficial network on the dorsal aspect of the posterior longitudinal ligament was seen to contain both nociceptive and sympathetic fibers.

This dorsal plexus formed a polysegmental innervating system by anastamoses from adjacent upper and lower fibers. A deeper network ventral to the posterior longitudinal ligament was seen to contain only nociceptive fibers. This deeper network did not form connections with adjacent levels at the level of the intervertebral disc, thereby making this ventral network unisegmental in innervation.

Another study has also promulgated a possible alternate pathway for return of annular sensory nerve fibers through the sinuvertebral nerve, rami communicants, and the lumbar sympathetic trunks.
This is in contrast to traditional belief that sensory nerve fibers only traveled afferently through the ventral rami, instead of rami communicants and lumbar sympathetic trunk.

Based on current data, it is evident the intervertebral disc has a rich nerve supply in its lateral portion.

These nerve fibers cover the superficial aspect of the disc and penetrate the annulus to a minimal extent. Thick networks of nerve fibers innervate the posterior longitudinal ligament. This network probably involves a large amount of cross-innervation between neighboring levels.
This complex network would then give each posterior longitudinal ligament a diffuse, poly-segmental innervation.

In addition, there may exist poly-segmental pathways in which these fibers may return to the spinal cord. The ventral dura also contains a rich polysegmental innervation of both autonomic and nociceptor fibers.

This diffuse innervation to the contents of the anterior spinal canal highlights the difficulty of diagnosing the etiology of low back pain.

SYMPATHETIC SYSTEM AND PAIN

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REVIEW ARTICLE

Visceral afferents: their contribution to 'sympathetic dependent' pain

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The accepted concept of 'sympathetic dependent' pain.

In this critical review, the evidence for this assumption is assessed.
It is found that the clinical phenomena suggesting sympathetic nerve involvement may be more satisfactorily attributed to effects of neuropeptides released from afferent C-fibres.

The relationship between visceral afferents, somatic afferents and autonomic efferents is outlined, and support is found for the unitary nature of the sensory system envisaged by Langley.

..visceral afferents can, at least on occasions in man, mediate pain not considered typically 'visceral'.

Current evidence supports Langley's (1903) classical concept of a **single sensory system that comprises afferents which travel both within somatic and autonomic nerves.**

Terminology

The nomenclature of afferent neurons within autonomic nerves is ambiguous (Lewis and Kellgren, 1939). This is because the terms sympathetic and parasympathetic are given to efferent systems contained in autonomic nerves, the fibres of which synapse in autonomic ganglia.
As shown by the evidence discussed below, however, **there are also afferent fibres subserving sensation which course with these efferent nerves; they are fellow-travellers whose ganglia lie in dorsal root ganglia**.
These afferents include those arising not only from the viscera, but also from peripheral structures, especially blood vessels. They have sometimes been called sympathetic, parasympathetic or generically autonomic afferents, terms accepted by numerous authors including Foerster *et al.* (1929), Kuntz (1951), Mitchell (1956), and Malliani (1982) who also comments on the history of the terminology. The autonomic nervous system, however, is by definition efferent, a difficulty which would be overcome by the term 'visceral afferent'.

In this paper, *the term 'visceral afferent' is used in that general sense for afferents that travel within autonomic nerves; such afferents innervate not only the internal body organs but also peripheral structures including in particular, but not exclusively, the peripheral vascular system.*

Pain and involvement of the sympathetic nervous system

The role of the sympathetic nervous system in certain human pain states has been envisaged and restated for 80 years. This is for two reasons:
- First, certain of these painful states, typically causalgia and reflex sympathetic dystrophy, may be accompanied by clinical features often associated with sympathetic disorders: disturbances of vasomotor, sudomotor and thermal functions, and trophic changes.
- Secondly, blocking the sympathetic supply to the affected part may relieve the pain (for reviews, *see* Bonica, 1979; Nathan, 1983; Schott, 1986, 1992a; Gybels and Sweet, 1989; Janig and Schmidt, 1992).

In many diseases, somatic and autonomic fibres within the same nerve will be affected together; effects mediated by any specific neural system may therefore prove difficult to delineate, an aspect considered further below. *The sympathetic nervous system itself, however, appears normal in patients with 'sympathetic dependent' pain.* Thus some patients with causalgia have no evidence of sympathetic dysfunction, although their pain may respond to sympathetic blockade (Loh and Nathan, 1978); there are no consistent changes in sympathetic function of the affected part in causalgia (Tahmoush *et al.,* 1983); and *patients with reflex sympathetic dystrophy have normal sympathetic function as assessed microneurographically* (Wallin *et al.,* 1976; Cline *et al.,* 1989; Torebjork, 1990).

The lack of specificity of 'sympathetic' blockade.

In the case of surgical interruption of the sympathetic outflow to a region and perhaps also after local anaesthetic and chemical blockade, it is difficult to determine underlying mechanisms.
This is because both afferent and efferent nerve functions, including sympathetically mediated modalities, are affected non- selectively.

A century ago, Langley stated that 'the afferent nerves of the sympathetic system are indistinguishable in form and position from those of the somatic system' (Langley, 1903). This view was reiterated by Lewis and Kellgren (1939) following studies on **referred pain**:

'. . . the pain of visceral and somatic disease is derived from the direct stimulation of a common system of pain nerves', and 'pain of visceral and somatic origin cannot be distinguished as such'.

Yet apart from sensory fibres innervating the viscera, and compared with somatic afferents, little attention has been given to sensory fibres travelling within autonomic nerves and which, too, might subserve pain. The terminology of visceral afferents has been referred to above.

A number of clinical observations support the concept that visceral afferents subserve pain:

(i) diseases of the autonomic nervous system are painless;
(ii) damage to autonomic nerves can generate pain-and a number of conditions illustrating this phenomenon are briefly described;
(iii) pain from diseases which involve autonomic nerves is improved by sympathetic blockade;
(iv) diseases which impair the function of visceral afferents predictably can result in impaired pain appreciation.

The relationships between visceral afferents and other neural pathways

Visceral afferents do not subserve pain in isolation. Somatic afferents, the other component of Langley's unitary sensory system, are closely related to visceral afferents, as are these afferent systems to autonomic efferents. The close proximity of these systems to one another would enable modulation of sensory input to occur, which may have major implications for nociception. It is also of interest that both dorsal root and sympathetic ganglia have in common an unusual vascular supply, characterized by lack of a blood—nerve barrier (Jacobs, 1980)

The evidence above thus demonstrates the close relationship between autonomic and somatic afferents, and between afferents and autonomic efferents.

The nervous system is also closely related to non-neural systems, in particular the peripheral vasculature. Apart from effects that result from changes in the local blood supply, **the innervation of blood-vessels has implications for pain-subserving mechanisms.**

The autonomic and somatic innervation of blood-vessels

The afferent innervation of blood-vessels is of considerable importance, because of the vessels' almost ubiquitous presence and because they provide an alternative network along which afferent neurons can travel from the periphery. **The innervation of blood-vessels consists of autonomic and sensory fibres containing numerous neurotransmitters: substance P , A TP , CGRP and neurokinin A**

Afferents supplying proximal vessels mainly reach the central nervous system through autonomic pathways and more distal vessels are innervated through pathways, that travel with somatic nerves or proximally along blood vessels (see Foerster *et ah,* 1929)

Furthermore, **although there is an intimate relationship between the nervi vasorum and the blood supply, the function of visceral afferents subserving sensation is independent of the state of the peripheral vasculature.**

This lack of correlation between nociception and blood supply is illustrated by various clinical observations: causalgia being observed, and relieved by sympathetic block, regardless of the vascular state of the affected part (Shumacker *et ah,* 1948); the relief of pain by sympathectomy despite the artery being permanently thrombosed (cited in Shaw, 1933);

The autonomic and somatic innervation of blood-vessels

Pain may also arise from veins.

This too may be relieved by sympathetic blockade, even in veins as peripheral as the saphenous vein, and relief of pain from both deep and superficial venous thrombosis may be 'immediate' and long before fever and oedema settle (Pereira, 1946; Parke and Chalmers, 1957).
These observations again confirm that relief occurs through mechanisms other than those related to blood flow and through an effect on sensory pathways.
That these pathways sometimes traverse sympathetic nerves is demonstrated by the observations that pain from stimulation of veins in the leg can be abolished by lumbar sympathetic block (Pereira, 1946).

Experimental evidence in man that afferents subserving pain travel with autonomic nerves

Whilst this suggests that somatic afferents are the sole pain-subserving pathway, many reports provide contrary evidence. For example, stimulation of the stellate ganglion and chain can produce pain in the face (Frazier, 1928), axilla and chest (including pain resembling angina) (Shaw, 1933; Leriche, 1939; White, 1954); stimulation of the coeliac plexus can produce pain in the abdomen; pain can be felt in the lower abdomen on stimulation of the LI ganglion, and in the leg on stimulation of the sympathetic ramus (Arnulf, 1948). Phantom pain has also been induced by electrical or mechanical stimulation of the lumbar sympathetic chain (Echlin, 1949).

Of importance is that there was a latency of some seconds before this extremity pain developed, suggesting an indirect, chemically mediated mechanism rather than a direct, electrically induced effect of stimulation.

Not only may stimulation of autonomic nerves produce pain, but conversely, pain persisting in an area in which the somatic innervation has been interrupted may be abolished by sympathetic block. Thus in a patient with complete cord section at L 1 , causalgia persisting in the legs was relieved by sympathectomy (Slaughter, 1938); cervical sympathectomy has abolished facial pain persisting after trigeminal anaesthesia (Harris 1936); pain persisting in the deafferented upper limb has been relieved by cervico-dorsal sympathectomy (White and Smithwick, 1941). As discussed above, these pain-subserving afferents may gain the central nervous system by travelling along perivascular pathways, consistent with the observations that arteries remain sensitive to mechanical stimuli in areas made anaesthetic following cord transection (Leriche, 1939) or spinal anaesthesia (Haugen, 1968)

Clinical implications of nociceptive afferents travelling with autonomic nerves

Four predictions follow from the suggestion that visceral afferents sometimes subserve pain, including causalgia, reflex sympathetic dystrophy and other 'sympathetically maintained' pains, as well as more classical visceral pain. These predictions are:

(i) Diseases which solely affect the autonomic nervous system would not cause pain.
(ii) Pain could be caused by iatrogenic damage to autonomic nerves due to simultaneous damage to fellow-travelling afferents.
(iii) Pain caused by diseases that involve visceral afferents could be improved by block of sympathetic nerves, since blockade would also interrupt afferents.
(iv) Disorders associated with impaired function of visceral afferents might be unexpectedly painless.
These predictions, which are confirmed by a wealth of clinical observations considered below, strongly support the involvement of visceral afferents as mediators of pain.

(i) *Diseases affecting solely the autonomic nervous system would not cause pain*

Neither pain nor analgesia is associated with diseases which selectively impair autonomic function, whether dysfunction is central or peripheral, or even segmental (Johnson and Robinson, 1987). Furthermore, diseases associated with increased sympathetic activity, such as hyperthyroidism and phaeo- chromocytoma, are also painless. These features contrast with those diseases of the autonomic nervous system in which afferents are also involved, as in more generalized neuropathic processes. In these, pain may develop or be inappropriately absent, and due to coincident involvement of other nerve types, sympathetic, sensory and motor dysfunction often occurs and has led to confusion when considering causalgia and similar states.

(ii) *Pain from iatrogenic lesions of autonomic nerves*

Whilst lesioning of the sympathetic outflow is undertaken for treatment of various painful conditions, the same procedures are also undertaken for painless conditions such as hyperhydrosis and vasospastic disorders. Paradoxically, a number of pain states may develop after such procedures. Whilst major sensory or motor loss is not seen unless coincidental somatic nerve damage occurs, hyperpathia and allodynia often accompany the pain, again recalling the question as to whether these sensory disturbances are characteristic of dysfunction of visceral afferents.

Visceral afferents and the central nervous system

Most information on human pains, including those subserved by autonomic afferents, comes from peripheral disorders. Of great importance are the central sequelae that follow peripheral lesions, since deafferentation leads to rapid, extensive and sometimes long-lasting changes throughout many parts of the central nervous system (for review, *see* Coderre *et al.,* 1993). Although functional separation between the peripheral and central nervous system is therefore imprecise, there are several phenomena mediated by the central nervous system in which visceral afferents contribute and which are relevant to human pain states.

The central termination of autonomic afferents: clinical implications

The central terminations of peripheral, perhaps pain-subserving visceral and somatic pathways have been much studied. An important demonstration of these central terminations was reported by Sugiura *et al.* (1989). These authors showed in an elegant study in animals that individual visceral afferent C-fibres traced into the spinal cord terminated in laminae IV, V and X as well as in the superficial dorsal horn (laminae I and II), extended for considerable distances up and down in the cord and also crossed the midline. The central processes of somatic afferent C-fibres terminated mainly in substantia gelatinosa (laminae I and II). This study therefore confirmed morphological overlap of physiologically identified visceral and somatic C-fibre inputs, demonstrating in animals an anatomical basis for referred pain in humans. The extensive central terminations of visceral afferents might also account for the often widespread, non- dermatomal and diffuse spread, and the bilateral clinical phenomena sometimes seen following initially unilateral painful conditions such as causalgia and related conditions (Kozin *et al., 1916a,b).* This contrasts with the precise sensory changes that can often be mapped in the periphery following isolated peripheral nerve lesions. In addition, central pain would be both explicable and expected when direct or indirect damage involved the central terminations of visceral afferents. The diffuse and extensive central terminations, and interactions possible with other systems, particularly at spinal level, would also account for the various autonomic and motor phenomena (Schott, 1992&) that can occur in the affected area.

Referred pain

Central convergence of afferents, including visceral and somatic inputs, is often invoked as an explanation for referred pain (for review, *see* Procacci *et al.,* 1986); peripheral mechanisms such as branching fibres, which supply both somatic and visceral structures, remain another possibility. Whilst referral of visceral disease to somatic structures is very well recognized, the reverse may also occur: pain from somatic disease can closely simulate visceral disease (Kellgren, 1940), a phenomenon that has recently been studied in further detail. Thus using microneurography, stimulation of the median nerve at the wrist can induce deep pain felt in the ipsilateral arm, axilla and chest (Torebjork *et al.,* 1984); whether visceral afferents would have been stimulated during this procedure is unclear. Since, however, referred pain can persist not only after somatic innervation has been blocked (Morley, 1929), but also be abolished by sympathetic blockade (Procacci *et al.,* 1986), probably both visceral and somatic afferents can subserve referred pain. Once again, this dual innervation mediating pain can be demonstrated.

Silent afferents

These newly identified unmyelinated primary sensory neurons have been identified in all tissues examined in a number of species including monkey, and can represent >50% of the unmyelinated population of fibres in certain tissues. Identified in skin, joint, muscle and viscera, these afferents develop a sensitivity which makes them responsive, but only following long-lasting damage as might occur with chronic injury or inflammation. Recent evidence obtained by microneurography has confirmed the same phenomenon occurs in man (Torebjork, 1993). If a proportion of these 'silent afferents' travel within autonomic nerves, contributing to the large proportion of small- diameter fibres in autonomic nerves, they would be susceptible to sympathetic blockade.

The effects of tissue damage: activation of 'silent' and visceral afferents and production of chronic pain ?

Although there are exceptions such as the pain of bladder fullness, it is generally damage and disease, numerous examples of which have been cited previously, which make visceral afferents eloquent. Chronic damage to more peripheral structures too can cause activation of 'silent' nociceptors, and presumably cause pain.
One example of this phenomenon is that of joint pain. It illustrates the interrelationship between somatic and visceral afferents {see Kidd *et al.,* 1992), and is also noteworthy since the joint was the first structure in which the role of 'silent' afferents was identified (Schaible and Schmidt, 1985). It is an everyday experience that movements of a joint within its physiological range are painless. After a sprain or in arthritis, however, even minor movements are painful, and the overlying tissues may show hyperpathia and allodynia amongst other local changes. These features, consistent with data from animal studies, point to the role of tissue damage in sensitizing afferent nerves from joints (Kidd *et al.,* 1990). If activation of 'silent' nociceptors occurs and their afferent fibres travel with sympathetic nerves, sympathetic blockade might relieve pain-and indeed this has been reported: both sympathectomy (Kidd *et al.,* 1992) and regional intravenous guanethidine injections (Levine *et al.,* 19866) may be beneficial for the pain of rheumatoid arthritis. Similarly, sympathetic blockade has been described in the control of pain from osteoarthritis of the hip (Kiaer, 1950).

The effects of tissue damage: activation of 'silent' and visceral afferents and production of chronic pain ?

Finally, there are chronic clinical disorders in which visceral pain can be transiently rekindled by experimental chemical or mechanical stimuli. Thus intravenous adenosine can briefly induce the typical epigastric pain of duodenal ulceration, but only in those with a confirmed ulcer (Watt *et al.,* 1987). In another example, unlike patients with stenotic coronary artery disease, patients with angina but normal coronary arteries may be sensitive to intracardiac movements of the catheter within the right atrium (Shapiro *et al.,* 1988). In a third example, abdominal pain induced by colonoscopy is felt more widely and also in extra-abdominal sites in patients with pain and irritable bowel syndrome compared with painfree individuals, and can also reproduce their presenting pain (Swarbrick *et al.,* 1980). These examples again show that disease can remain virtually painless until specific local stimuli initiate pain, perhaps activating both pain-subserving visceral and 'silent' afferents.

CONCLUSION

Confusingly, since they travel within the same autonomic system, the evidence presented above suggests that it is afferents which travel within sympathetic and parasympathetic nerves, and which may generically be termed **visceral afferents, which mediate many of these painful states**. Analogous to pain caused by damage to somatic nerves, damage to previously normal visceral afferents can generate pain and perhaps also cause allodynia and other sensory disturbances. Diseases or procedures that impair the autonomic outflow and relieve pain may do so, not by effects on sympathetic efferent neurons, but by blocking those visceral afferent fibres within the autonomic system. *Visceral afferents are usually clinically silent, and generally only subserve pain when damaged*. These properties are reminiscent of the recently described 'silent afferents', which might subserve pain that hitherto and perhaps mistakenly was considered to be 'sympathetically maintained'. Numerous examples illustrate that, in addition to the well-known instances of classical visceral pain, **visceral afferents can subserve many different forms of pain, and contribute to the various phenomena that accompany it**. The present observations proposing involvement of visceral afferents provide a more satisfactory explanation for 'sympathetic dependent' pain seen in man, and support the concept of the unitary nature of the sensory system envisaged by Langley a century ago

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An Anatomic Study of Neuropeptide Immunoreactivities in the Lumbar Dura Mater After Lumbar Sympathectomy

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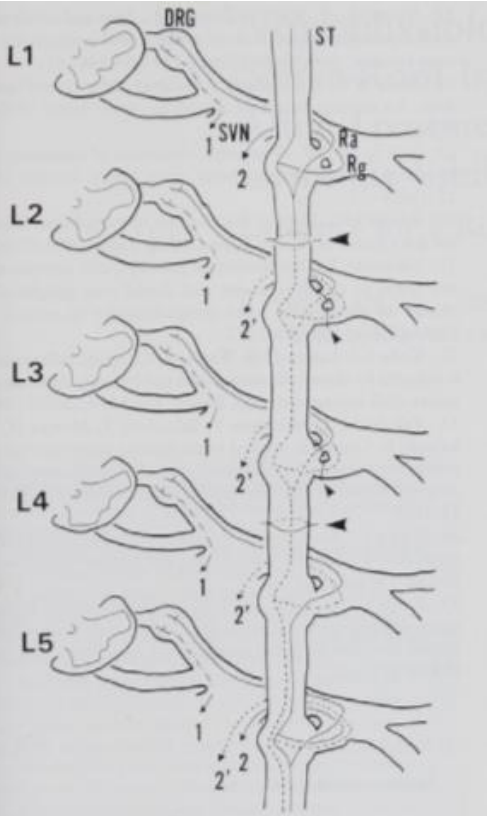

Figure 8. A schematic illustration of calcitonin gene-related peptide immunoreactive (CGRP-IR) fibers' pathway to the lumbar dura mater. Two pathways of CGRP-IR fibers to lumbar dura mater were considered. First pathway is direct innervation from dorsal root ganglia (1). The second is a fiber descending through the sympathetic trunk (2). In the present study, L2-L3 sympathectomy reduced the fibers (shown by dotted line) passing through sympathetic trunk. Fibers (2') innervating to lumbar dura mater were reduced associated with transection of the sympathetic trunk. In this illustration, the authors did not describe the participation of sympathetic nerves to sensory nerves. DRG = dorsal root ganglion. SVN = sinuvertebral nerve. ST = sympathetic trunk. Ra = ramus albus. Rg = ramus griseus. 1. Fibers directly innervated from DRG. 2. Fibers passing through sympathetic trunk. 2'. Fibers transected by sympathectomy from L2 to L3. Arrowheads indicate the transected sites.

It is well known that the number of CGRP cells in dorsal root ganglia decreased after transection of main nerve fibers.[26] In the present study, the CGRP cells did not decrease quantitatively regardless of the apparent decrease of the CGRP fibers in the lumbar dura mater. This phenomenon indicates that the participation of the nerve fibers in the lumbar dura mater may be too small to degenerate the original cells, *i.e.*, dorsal root ganglia cells, or the number is too few to detect degenerated cells after sympathectomy in the quantitative analysis. However, CGRP fibers in the lumbar dura mater are passing through the lumbar sympathetic trunk (Figure 8).

The authors' observation in this experiment may imply that upper lumbar sympathetic trunk (L2–L3) modulates nociception of the sensory nerve in the hind legs. Consequently, the authors' results indicated that sympathetic trunk contributed to the pain mechanisms involving low back pain or pain of lower extremities.

These experimental findings coincide with the clinical reports that L2 dorsal root ganglia or sympathetic block relieves low back pain elicited by L3–L4, L4–L5 disc herniation.[25,33]

Sympathetic afferent units from lumbar intervertebral discs

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To clarify the pathomechanisms of discogenic low back pain, the sympathetic afferent discharge originating from the L5-L6 disc via the L2 root were investigated neurophysiologically in 31 Lewis rats. Sympathetic afferent units were recorded from the L2 root connected to the lumbar sympathetic trunk by rami communicantes. The L5-L6 discs were mechanically probed, stimulated electrically to evoke action potentials and, finally, treated with chemicals to produce an inflammatory reaction. We could not obtain a response from any units in the L5-L6 discs using mechanical stimulation, but with electrical stimulation we identified 42 units consisting mostly of A-delta fibres. In some experiments a response to mechanical probing of the L5-L6 disc was recognised after producing an inflammatory reaction. This study suggests that mechanical stimulation of the lumbar discs may not always produce pain, whereas inflammatory changes may cause the disc to become sensitive to mechanical stimuli, resulting in nociceptive information being transmitted as discogenic low back pain to the spinal cord through the lumbar sympathetic trunk. This may partly explain the variation in human symptoms of degenerate discs.

Discussion

It has been reported that visceral and somatic primary afferent fibres had receptive fields in the low back region and projected stimuli centrally through the lumbar sympathetic trunk.

However, these studies have not demonstrated that the intervertebral discs themselves are the source of the low back pain. Using neurophysiological methods, this experiment has confirmed the presence of a sensory pathway of sympathetic afferent discharge from the dorsal aspect of the lower lumbar intervertebral discs to the dorsal roots of L2.
Conduction velocities were estimated from latencies evoked by bipolar electrical stimulation and the distance between the recording electrode and the point of electrical stimulation on the L5-L6 discs. This procedure lacks accuracy, possibly because the course of the afferent axons could not always be exactly determined. Nevertheless, we could not identify unmyelinated fibres with conduction velocities less than 2 m/s possibly due to insufficient intensity of electric stimulation for evoking unmyelinated fibres.

In general, **lumbar intervertebral discs have been considered as one of the major sources of low back pain. There is growing evidence that sympathetic afferents play a significant role in low back pain.**

Nakamura et al15 reported a study of 33 patients in whom infiltration of the L2 nerve roots with lidocaine relieved low back pain originating at the lower lumbar levels.

On the basis of their previous neuroanatomical study, in which lumbar discs were found to have innervation from the sympathetic trunk, it was suggested that **lumbar discogenic pain was a variety of visceral pain**.

Additionally, in the experimental setting, electrical stimulation of the lumbar sympathetic trunk has provoked low back pain16 and, conversely, lumbar sympathetic block reduced low back pain.17

The present study also showed that afferent signals originating from the L5-L6 intervertebral disc passed through the lumbar sympathetic trunk into the L2 roots and further into the spinal cord. These results suggest that lumbar discogenic pain is closely connected with the sympathetic afferent system.

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Our experiment demonstrated that the L5-L6 intervertebral discs were not responsive to mechanical stimulation under normal conditions, but once inflamed by the application of carrageenan, some of these mechanically insensitive afferents did respond to mechanical stimulation.

Mechanically insensitive afferents have been shown to become responsive to stimuli under pathological conditions such as inflammation in joints, viscera and the cornea.

The receptors of mechanically insensitive afferent fibres are referred to as silent nociceptors and account for approximately half of the A-delta and 30% of the C-fibre nociceptor.
These silent nociceptors have been described in the digestive system, related to the autonomic nerve fibres that partially pass through the sympathetic chain. The afferent fibres innervating the colon became sensitised to mechanical stimuli during inflammation. The findings of our study strongly suggest that the receptors of the intervertebral discs are silent nociceptors, which are activated under inflammatory conditions and modulate nociceptive information.

Kuslich, Ulstrom and Michael found that mechanical stimulation of the annulus of an affected disc during low back operations, conducted under local anaesthesia, provoked significant pain in approximately two-thirds of the symptomatic patients. However, the absence of pain in the remaining one-third remains unexplained.

Similarly, discography conducted in a group of asymptomatic patients caused pain in only 10%.
To explain these clinical phenomena requires characterisation of the sensory information originating from the lower lumbar intervertebral discs, which is transmitted to the central nervous system. Recently, nerve growth has been found in granulation tissue in the fissures of degenerated discs.

Our results may be a plausible explanation as to why mechanical stimulation to lumbar discs does not always produce pain. Inflammatory changes may cause the silent nociceptors to become responsive to mechanical stimuli, and this nociceptive information is transmitted as discogenic low back pain to the spinal cord through the sympathetic trunk.
It remains to be resolved how disc degeneration not associated with inflammation is correlated with low back pain.

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Neuroanatomy, Autonomic Nervous System Visceral Afferent Fibers and Pain

Authors

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Structure and Function

GVA fibers are primarily pseudounipolar neurons; they initially develop as bipolar neurons before altering their morphology to resemble unipolar neurons. During development, the two processes emerging from the cell body fuse to form a single continuous process with a distal and proximal point, between which lies the cell body. The cell body of a GVA fiber can be found somewhere along a cranial nerve or in the dorsal root of the spinal cord. These GVA cell bodies are, for the most part, extracranial, except for the GVA fibers of the trigeminal nerve, whose nucleus lies within the brainstem. The cell body controls all neuronal functions and allows information to pass between the receptive distal part and the centrally projecting part.

Visceral afferent fibers are supported by Schwann cells, a type of glial cell that supplies nutrients to peripheral nerves and has a role in nerve regeneration. Schwann cells also insulate (myelinate) the axons of neurons from the peripheral nervous system by forming the myelin sheath. This sheath is not continuous, leaving unmyelinated gaps along the axon called nodes of Ranvier. Together, the myelin sheath and nodes of Ranvier improve the axonal conduction velocity resulting in a faster response time.

Three types of sensory receptors can activate GVA fibers: mechanoreceptors, nociceptors, and chemoreceptors. Each of these receptors detects a specific stimulus associated with a different set of nerve fibers. Mechanoreceptors respond to mechanical pressure or physical deformation.They receive their innervation through type II or III A-delta sensory fibers. Nociceptors detect pain and are innervated by type III and IV C fibers. Chemoreceptors detect chemical changes (ie, pH, carbon dioxide, and oxygen levels).Cranial nerves innervate this latter receptor type.

Nerves

Once the sensory receptor is activated, the GVA impulse travels through the pseudounipolar neurons to reach the CNS. When the GVA fiber reaches the dorsal horn of the spinal cord, it terminates on a second-order neuron. These neurons then ascend upwards into the brain for further processing. Under normal circumstances, visceral afferent activity does not reach the level of consciousness. However, if the visceral afferent activity is pain-related, it can reach the level of consciousness. Visceral pain is frequently felt in an area remote from the location of the affected organ; this is known as referred pain. The chart at the end of this article provides more information about where referred pain appears for specific organs.

Muscles

Stimulation of GVA fibers influences the motor response of their respective GVE fibers. These visceromotor fibers innervate either smooth muscle, cardiac muscle, or glands.

Oxford Handbooks Online

The Sympathetic Nervous System and Pain

Judith A. Strong, Jun-Ming Zhang, and Hans-Georg Schaible

The Oxford Handbook of the Neurobiology of Pain
Edited by John Wood

Subject: Neuroscience, Molecular and Cellular Systems Online Publication Date: Jul 2018
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The interactions between the sympathetic nervous system and the immune system as they relate to pain. Some of the earliest preclinical studies of sympathetically regulated pain focused on sympathetic–sensory neuron interactions, and even recent clinically oriented studies often focus on this aspect (e.g., Liao, Tsauo, Liou, Chen, & Rau, 2016). However, the more recent understanding of the importance of interactions between the immune and sensory nervous systems on one hand (Foster, Seehus, Woolf, & Talbot, 2017), and interactions between the sympathetic and immune systems on the other (Jänig, 2014), leads us to propose that understanding sympathetic effects on the immune system will prove fruitful in understanding sympathetically regulated pain.

Aspects of Sympathetic Anatomy and Physiology Relevant to Pain

Basic textbook descriptions of the autonomic nervous system often emphasize the dual innervation of various structures by the sympathetic and parasympathetic nervous systems, usually with opposing effects. Hence, the sympathetic effects on structures such as the heart (increasing rate and force of contraction), iris (pupil dilation), and digestive tract (inhibition of peristalsis) are generally the opposites of the parasympathetic effects. However, in considering the role of the sympathetic system in pain, it is perhaps especially relevant to consider some of the targets and effects not generally emphasized in the basic textbook descriptions of the autonomic nervous system. Often, these targets lack parasympathetic innervation. An important example is the sympathetic innervation of primary and secondary immune tissues, which may indirectly affect pain (Figure 1).

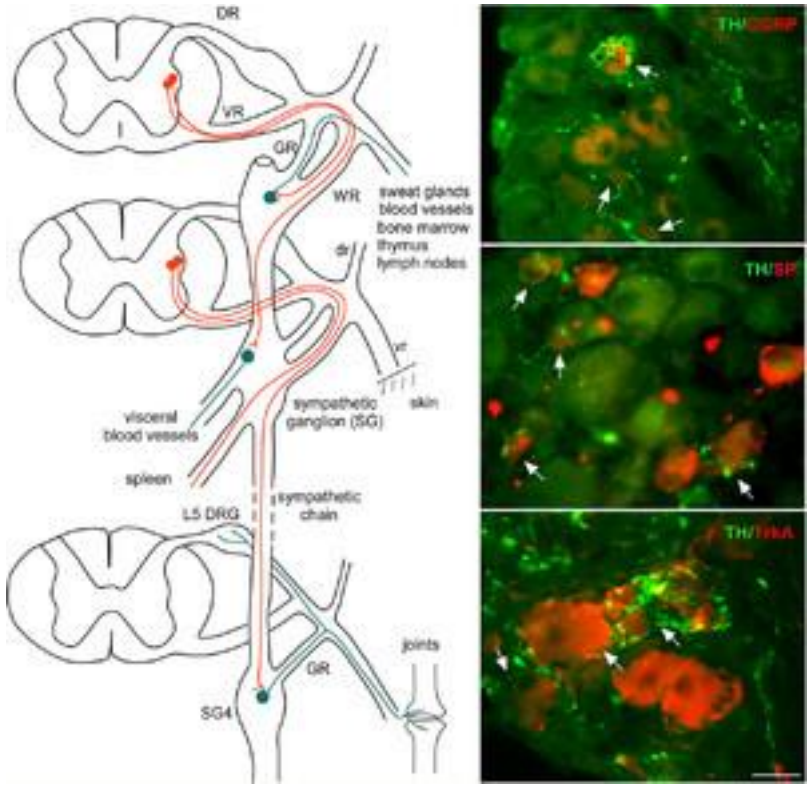


Figure 1 Interactions of the sympathetic nervous system and the sensory nervous system in pain and inflammation. Left: Schematic diagram of sympathetic system in association with the sensory nervous system. Sympathetic preganglionic neurons (red) have cell bodies in the intermediolateral cell columns of the spinal cord. Their axons leave the spinal cord through the ventral roots (VR) and follow white rami (WR) to the paravertebral sympathetic ganglion (SG) chain. Some make synapses with postganglionic neurons (green) in the paravertebral sympathetic ganglia, either at the same level, or at other levels after projecting in the sympathetic chain. Axons of some preganglionic neurons pass through chain ganglia without synapsing and connect with postganglionic neurons in prevertebral or pelvic ganglia. Some target tissues discussed in the chapter are indicated. At the lumbar levels below L3, there are no white rami, as preganglionic neurons are found in more rostral spinal cord regions. Here, postganglionic axons, primarily from SG neurons in SG3 or SG4, run through the gray ramus (GR) to the spinal nerve, where they may project along the ventral ramus (vr) of the spinal nerve to enter the sciatic nerve and reach peripheral targets, or project into the dorsal ramus (dr) of the spinal nerve, or innervate the region around the lumbar DRG itself (primarily innervating blood vessels and the surface). Right: Representative examples of DRG sections showing nociceptive markers in cells with and without sympathetic contacts after the spinal nerve ligation pain model. DRG sections were stained for the indicated marker (red) and for tyrosine hydroxylase (TH; green) on postoperative day 3. Arrows indicate examples of cells expressing the indicated marker along with sympathetic basket formations or nearby fibers.

Sympathetic innervation of primary immune organs (e.g., bone marrow, thymus) and secondary immune organs (e.g., lymph nodes, spleen, gut-associated lymphoid tissue) is characterized by close or even synaptic-like contacts between sympathetic nerve endings and immune cells (Bellinger & Lorton, 2014; Jänig, 2014; Takenaka, Guereschi, & Basso, 2017).

It has been proposed that the sympathetic neurons regulating these immune tissues may form a functionally distinct pathway, with distinct regulation and reflex patterns, analogous to the distinct pathways of the subsets of sympathetic neurons that regulate vasoconstriction or sudomotor responses.

For example, much of the sympathetic innervation of the spleen appears to be regulated differently than typical vasoconstrictor neurons are (Jänig, 2014).

Although our primary focus in this chapter is on the peripheral nervous system, a brief discussion of the control of the sympathetic nervous system by the central nervous system is in order.

The sympathetic postganglionic neurons are controlled by cholinergic preganglionic neurons with cell bodies located in the intermediolateral zone of the thoracolumbar spinal cord; in the prevertebral ganglia, they can also receive direct connections from collateral axons of visceral sensory neurons.
The postganglionic sympathetic cells are therefore the motor arm of spinal-level or local autonomic reflexes. In addition, these cells also are regulated by inputs from the brain stem and hypothalamus.
This descending information, integrated with spinal-level autonomic reflexes, coordinates complex reflex patterns regulating autonomic functions, with the effect of maintaining homeostasis and responding to internal or external threats. Higher brain centers (cortical and limbic) also participate in regulating the sympathetic output; an example is the activation by psychological stressors. The afferent limb of these systemic autonomic reflexes includes not only sensory (especially visceral) nerves and enteric nerves, but also systemic hormones and other humoral messengers such as cytokines or blood glucose levels. Some of these circuits, such as those involved in cardiovascular regulation, osmoregulation, and regulation of body temperature, are well understood. (Jänig, 2013, 2014). The putative central circuit regulating immune function is not as well studied, although systemic cytokines are known to play a role in signaling between the immune system and brain centers involved in regulating the sympathetic output to immune tissues. However, some studies have demonstrated regulation of neurogenic inflammation and dorsal root reflexes by sympathetic neurons occurring at the spinal level and in the periphery (Lin, Zou, Fang, & Willis, 2003; Svennsson & Sorkin, 2017).

Most sympathetic fibers release noradrenaline (norepinephrine) as their transmitter, which regulates target tissues through two classes of adrenoreceptors (α and β). However, a number of co-transmitters have been identified, including adenosine triphosphate (ATP), vasoactive intestinal peptide (VIP), and nitric oxide, which may themselves function as immune modulators (Pongratz & Straub, 2014). Since both sensory neurons and immune cells may express receptors not only for noradrenaline, but for these co-transmitters, the existence of co-transmitters may be an important consideration in designing studies of sympathetic regulation of pain. In particular, sympathetic regulation of a particular pain phenotype cannot be ruled out simply by showing that adrenergic blockade has no effect. Conversely, under some conditions, cell types other than the sympathetic nerves (and the adrenal gland) may serve as sources of noradrenaline.

Systemic versus Local Effects of the Sympathetic Nervous System on Immunity

The functional consequences of the sympathetic innervation of immune tissues are still being elucidated. In many, but not all, cases, the overall effect, especially at the systemic level, seems to be to suppress immunity and inflammation, but these effects vary with context in a complex way (Pongratz & Straub, 2014), and localized sympathetic effects may be more pro-inflammatory (Elenkov, Wilder, Chrousos, & Vizi, 2000). An example of a more systemic effect is the sympathetic innervation of the spleen, which suppresses natural killer cell activity (Jänig, 2014). Sympathetic innervation of the bone marrow increases release of hematopoietic stem/progenitor cells, which can then migrate to sites of tissue injury and differentiate into anti-inflammatory (type 2) macrophages (Jung, Levesque, & Ruitenberg, 2017). Many immune cells express receptors for noradrenaline, the primary sympathetic transmitter. In several types of immune cells, activation of the β class of adrenergic receptors drives an anti-inflammatory or type-2 immune response, while stimulation of α class receptors drives a pro-inflammatory response (Bellinger & Lorton, 2014). This suggests that the net effect of sympathetic stimulation of immune tissue may depend on what receptors are present, which may vary in different pathological states. This also makes it more difficult to extrapolate from in vitro studies of adrenergic stimulation of immune cells to the in vivo situation.

Systemic versus Local Effects of the Sympathetic Nervous System on Immunity

A study of sympathetic effects on neuroinflammation in the dorsal root ganglia (DRG) evoked by peripheral nerve transection showed that, although local sympathetic denervation (removal of the lumbar sympathetic ganglia nearest the DRG) reduced immune cell infiltration in the DRG, a more limited, isolated denervation of only the draining lymph node increased T-cell infiltration in the DRG (McLachlan & Hu, 2014). We will discuss other examples of this type of finding, in which local sympathetic innervation of a non-immune tissue (the DRG, in this case) is pro-inflammatory, while innervation of the immune tissue suppresses immune function. Other studies of sympathetic innervation of the lymph node also found that it served to inhibit emigration of lymphocytes (Madden, 2017).
The sympathetic innervation of blood vessels may also have effects on immunity and inflammation, and hence on pain, not only through their regulation of blood flow, but through their effects on vascular permeability and on immune cell trafficking between blood and tissue

Trafficking of immune cells across the endothelium into the tissues is regulated by intercellular adhesion molecules, whose expression is increased by sympathetic nerve activity. This effect contributes to increased immune cell recruitment during local inflammation (Mousa et al., 2010) and accounts for the circadian rhythm in recruitment (Scheiermann et al., 2012).
A final example of a "non-classical" sympathetic innervation is the presence of free sympathetic nerve fibers in, for example, the skin, joints (see following), and even on the surface of the DRG (Xie, Strong, & Zhang, 2010; see Figure 1). It has been proposed that sympathetic fibers in the skin that do not innervate "classical" targets such as arterioles and sweat glands may play a role in regulating immunity (Jänig, 2014). In general, the function of these fibers is poorly understood, but as discussed in greater detail later, they may have important modifying effects on pain.

Sympathetic Role in Other Inflammatory Pain Models

Low back pain conditions often include an element of local inflammation in the region of the DRG.

Preclinical studies have shown that surgical sympathectomy (removal of lumbar sympathetic ganglia) reduced pain behaviors in several rat models of low back pain (Iwase et al., 2012; Murata, Olmarker, Takahashi, Takahashi, & Rydevik, 2006; Ogon et al., 2015).
The Ogon et al. study (2015) also showed that pharmacological sympathetic blockade (α receptor antagonists injected around the DRG) was effective. These findings suggest that the sympathetic effects on pain may occur near the DRG.
Other findings supporting this idea include the findings that sympathectomy also reduced hyperexcitability of sensory neurons (Iwase et al., 2012), and the finding that even a "microsympathectomy"—that is, cutting the two gray rami by which postganglionic sympathetic axons enter the L4 and L5 spinal nerve and L4/L5 DRG regions—was highly effective in reducing both pain behaviors and sensory neuron hyperexcitability in a low back pain model induced by locally inflaming the L5 DRG (Xie et al., 2016).

In that study, microsympathectomy was also shown to mitigate the upregulation of type 1 pro- inflammatory cytokines and downregulation of type 2 anti-inflammatory cytokines induced in the DRG by the model.
In addition (more relevant to the clinical situation), microsympathectomy was also shown to be effective in reducing established pain behaviors when performed two weeks after the DRG inflammation.

Sympathetic Role in Other Inflammatory Pain Models

Models of peripheral inflammatory pain often involve injection into the rodent hindpaw of substances that induce inflammation (e.g., carrageenan, CFA) or tissue damage (e.g., formalin).

These models result in mechanical and/or thermal hypersensitivity and allodynia, as well as spontaneous pain.
Chemical or surgical (removal of lumbar sympathetic ganglia) sympathectomy reduced pain induced by bee venom injection into the paw (Chen, Qu, He, Wang, & Wen, 2010).
Pain behaviors in the CFA model were markedly reduced by cutting the gray rami at the L4 and L5 DRGs prior to paw inflammation (Xie et al., 2016). In both of those studies, paw swelling was also reduced by sympathectomy, suggesting a role for reduced inflammation in mediating the sympathectomy effects. However, very different results were obtained in another study, also using the CFA model, in which neonatal chemical sympathectomy had almost no effect on behaviors (Woolf, Ma, Allchorne, & Poole, 1996).

It seems likely that these conflicting findings may be related to the very different methods of sympathectomy used.

The CFA model induces sprouting of sympathetic fibers into the upper dermis (Almarestani, Longo, & Ribeiro-da-Silva, 2008; Yen, Bennett, & Ribeiro-da-Silva, 2006), although this occurs relatively slowly. The sprouted fibers are associated with sensory nerve endings rather than blood vessels. Induction of pain behaviors was reduced by systemic pharmacological sympathetic blockade in a model of peripheral inflammatory pain induced by paw injection of bacterial endotoxin (Safieh-Garabedian et al., 2002). In this study, reduction of endotoxin-induced upregulation of several pro-inflammatorycytokines by sympathetic blockade was observed, also suggesting an immune-system related mechanism.

Although pain models are conventionally characterized as neuropathic (involving damage to the nerves) or inflammatory, it is now recognized that neuropathic injuries always include a component that might be termed "inflammatory." These include tissue repair mechanisms that involve immune cell infiltration and activation, and activation of microglia in the spinal cord and satellite glia in the DRG (Moalem & Tracey, 2006). Hence, some of the discussion in the section on inflammatory pain models may conceivably pertain to neuropathic pain models. In humans, the neuropathic pain condition CRPS clearly has inflammatory and immune components, including upregulation of pro-inflammatory cytokines, increased neurogenic inflammation, and in some cases, auto-antibody production (Schlereth, Drummond, & Birklein, 2014). Because CRPS most often develops after a limb fracture, a rat model based on distal tibial fracture and casting has been developed, which mimics elements of early CRPS, including mechanical pain, edema, limb warmth, and bone changes (Guo, Offley, Boyd, Jacobs, & Kingery, 2004). In this model, chemical sympathectomy (implemented after the model was established) reduced mechanical pain and indicators of inflammation.

Possible Reasons for Discrepancies in Preclinical and Clinical Literature on the Effect of the Sympathetic Nervous System in Pain

As discussed before, there are often conflicting results in both preclinical and clinical literature about the role of the sympathetic nervous system in pain. Following, we discuss several possible factors that may contribute to this variability.

A common theme in clinical and preclinical literature is that the timing of a sympathetic intervention determines its effect on pain. More specifically, the sympathetic nervous system often has a pro-nociceptive role earlier in the disease, which may disappear or become anti-nociceptive at later stages. In human patients, it is plausible that equivocal findings regarding sympathetic interventions may be because there are subsets of responsive and unresponsive patients that are at different stages of disease progression. In light of the local pro-inflammatory role played by sympathetic activation in many studies, effectiveness of sympathetic interventions might also vary depending on the degree of inflammation present in a particular patient.

Possible Reasons for Discrepancies in Preclinical and Clinical Literature on the Effect of the Sympathetic Nervous System in Pain

As discussed before, there are often conflicting results in both preclinical and clinical literature about the role of the sympathetic nervous system in pain. Following, we discuss several possible factors that may contribute to this variability.

Global sympathectomy may give different results than more local methods of sympathectomy do. Because in many tissues the local sympathetic innervation seems to play a pro-inflammatory role, while sympathetic innervation of primary and secondary immune organs often has an anti-inflammatory or type-2 inflammation- skewing influence, it is likely that different effects on pain could be observed, depending on the method of sympathectomy. For example, localized denervation by cutting a few gray rami at the lumbar level, which was strongly anti-nociceptive in several pain models, might give different results than global sympathectomy using agents such as systemic injection of guanethidine or 6-hydroxy-dopamine. This is plausible because the more global sympathectomy methods might also evoke counteracting pro-inflammatory responses due to loss of innervation of immune tissue. Some chemical methods of sympathectomy may also affect non-neuronal cells that produce norepinephrine, in addition to the targeted sympathetic nerves (Madden, 2017; Pongratz & Straub, 2014). Lumbar surgical sympathectomy will denervate more structures than localized sympathectomy, but fewer structures than chemical sympathectomy.

Possible Reasons for Discrepancies in Preclinical and Clinical Literature on the Effect of the Sympathetic Nervous System in Pain

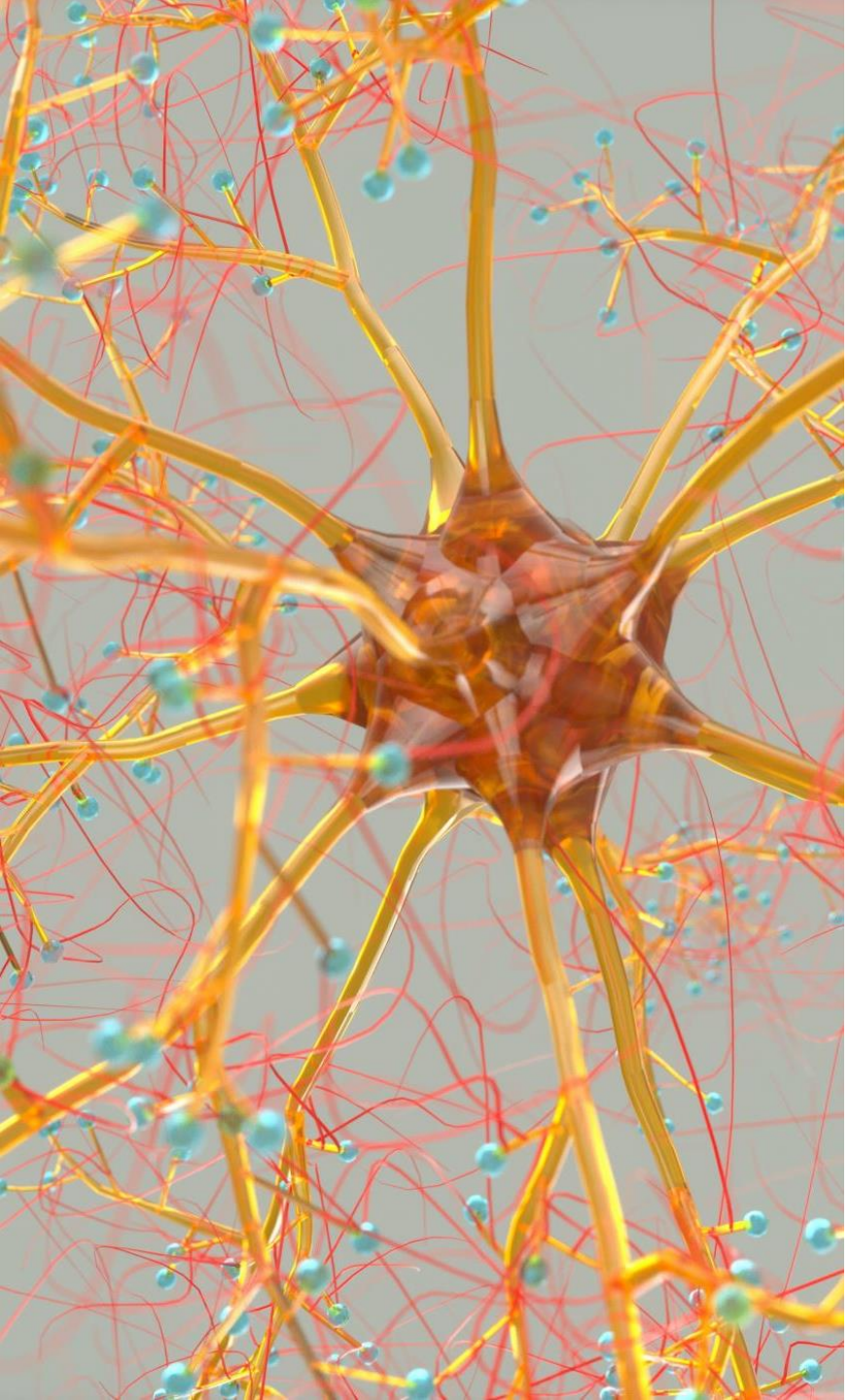
As discussed before, there are often conflicting results in both preclinical and clinical literature about the role of the sympathetic nervous system in pain. Following, we discuss several possible factors that may contribute to this variability.

Saturation effects in pain models used may obscure sympathetic effects. For example, mechanical pain in several of the neuropathic and inflammatory pain models mentioned almost reaches a floor value, which would make it difficult to show that a sympathetic innervation was further increasing pain.

Possible Reasons for Discrepancies in Preclinical and Clinical Literature on the Effect of the Sympathetic Nervous System in Pain

As discussed before, there are often conflicting results in both preclinical and clinical literature about the role of the sympathetic nervous system in pain. Following, we discuss several possible factors that may contribute to this variability.

An issue that has received relatively little attention is the possible modification of the sympathetic nerves by inflammation or nerve damage. A few studies have observed signs of neuroinflammation or hyperexcitability in the sympathetic ganglia in response to peripheral nerve damage or peripheral inflammation (e.g., Hu & McLachlan, 2004; Li, Zhang, Xie, Strong, & Zhang, 2017). Given the long-held view that sympathetic postganglionic fibers are only activated by the preganglionic fibers, and the classic studies showing that axotomized sympathetic postganglionic fibers lose their preganglionic inputs via synaptic stripping (Purves, 1975), it is not clear how blockade or removal of already axotomized sympathetic endings can further affect pain and inflammation. However, it is worth noting that spontaneous activity of sympathetic neurons has been observed in a systemic inflammation model (Lukewich & Lomax, 2015) and an intestinal inflammation model (Dong, Thacker, Pontell, Furness, & Nurgali, 2008). In addition, effects of sympathectomy on bradykinin-induced plasma extravasation in joints are not mimicked by cutting the preganglionic fibers (Jänig & Green, 2014), suggesting that either activity in the sympathetic fibers is not required for the sympathetic regulation of extravasation, or the assumption that activity in postganglionic fibers only follows preganglionic activity is incorrect in some conditions. These examples suggest that studies of the effects of pain models and inflammation on the sympathetic system are needed to fully understand effects of the sympathetic system on pain and inflammation.



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The **autonomic nervous system (ANS)** consists of **general visceral efferent (GVE)** fibers that create a motor response due to **general visceral afferent (GVA**) fiber stimulation.

Although general visceral afferent fibers are part of the ANS, they are not classified as part of the sympathetic or parasympathetic system.
However, these visceral sensory nerves often colocalize within sympathetic and parasympathetic nerves

GVA fibers carry sensory impulses from internal organs to the central nervous system (CNS). Stimuli that activate GVA fibers include hunger, blood pressure, organ distention, and visceral inflammation

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Three types of sensory receptors can activate GVA fibers: mechanoreceptors, nociceptors, and chemoreceptors.
Each of these receptors detects a specific stimulus associated with a different set of nerve fibers.

- *Mechanoreceptors* respond to mechanical pressure or physical deformation. They receive their innervation through type II or III A-delta sensory fibers.
- *Nociceptors* detect pain and are innervated by type III and IV C fibers.
- *Chemoreceptors* detect chemical changes (ie, pH, carbon dioxide, and oxygen levels).

Cranial nerves innervate this latter receptor type.

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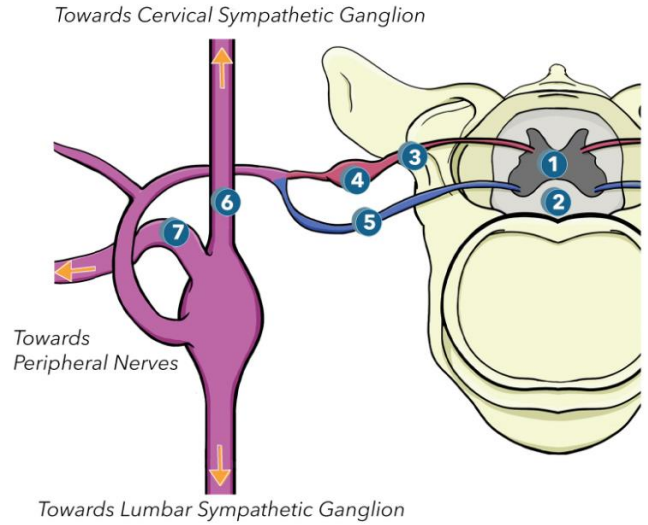
Once the sensory receptor is activated, the GVA impulse travels through the pseudounipolar neurons to reach the CNS.

When the GVA fiber reaches the dorsal horn of the spinal cord, it terminates on a second-order neuron.

These neurons then ascend upwards into the brain for further processing.

Under normal circumstances, visceral afferent activity does not reach the level of consciousness.
However, if the visceral afferent activity is pain-related, it can reach the level of consciousness.

Visceral pain is frequently felt in an area remote from the location of the affected organ; this is known as referred pain



Autonomic Nervous System Pathway Flow

1. Grey Matter
2. White Matter
3. Visceral Afferent Fibers
4. Dorsal Root Ganglion
5. Preganglionic Sympathetic Fibers
6. Sympathetic Trunk
7. Peripheral Nerve

Neuroanatomy, Autonomic Nervous System Visceral Afferent Fibers and Pain

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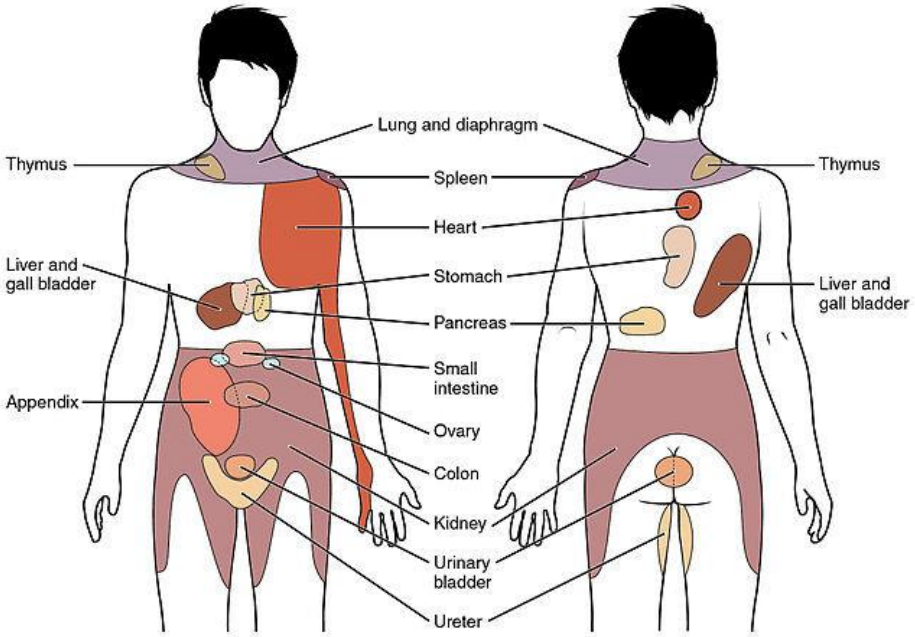
Current knowledge indicates that referred pain occurs because multiple primary sensory neurons converge on a single ascending tract in the spinal cord. When painful stimuli activate visceral receptors, the brain is unable to distinguish between the visceral signals and somatic signals; the brain interprets that the pain is coming from somatic regions (e, skin, skeletal musculature, and bones) of the body rather than the visceral regions (ie, spleen, kidney, and heart). For example, patients with angina pectoris, a type of cardiac pain, experience referred pain in the chest and upper left arm.



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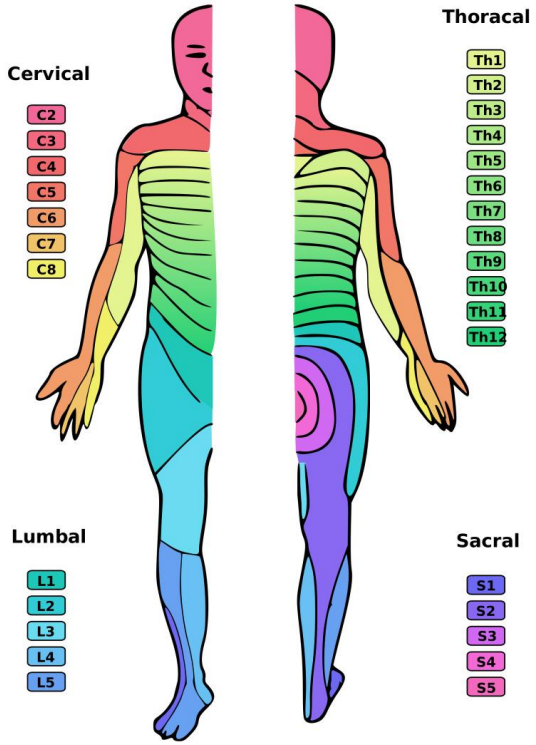

Another example is patients with temporomandibular disorder (TMD), who may experience referred pain in the teeth or other sections in the orofacial area. Areas of referred pain can be cross-referenced against dermatome charts to help identify the visceral organ sending pain signals.

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Muscles

Stimulation of GVA fibers influences the motor response of their respective GVE fibers. These visceromotor fibers innervate either smooth muscle, cardiac muscle, or glands.

Physiologic Variants

Receptors associated with GVA fibers will vary in sensitivity and affect the body's ability to maintain homeostasis. Upregulation or downregulation of these receptors will change the intensity of the signal propagated through the afferent fiber.

This intensity is of particular importance in the perception of referred pain.