

■ REVIEW ARTICLE

The nerve supply of the lumbar intervertebral disc

M. A. Edgar

From University College and The Middlesex Hospital, London, England

The anatomical studies, basic to our understanding of lumbar spine innervation through the sinu-vertebral nerves, are reviewed. Research in the 1980s suggested that pain sensation was conducted in part via the sympathetic system. These sensory pathways have now been clarified using sophisticated experimental and histochemical techniques confirming a dual pattern. One route enters the adjacent dorsal root segmentally, whereas the other supply is non-segmental ascending through the paravertebral sympathetic chain with re-entry through the thoracolumbar white rami communicantes.

Sensory nerve endings in the degenerative lumbar disc penetrate deep into the disrupted nucleus pulposus, insensitive in the normal lumbar spine. Complex as well as free nerve endings would appear to contribute to pain transmission.

The nature and mechanism of discogenic pain is still speculative but there is growing evidence to support a 'visceral pain' hypothesis, unique in the musculoskeletal system. This mechanism is open to 'peripheral sensitisation' and possibly 'central sensitisation' as a potential cause of chronic back pain.

During the last two decades many anatomical and experimental studies have provided much information about the innervation of the normal and degenerative lumbar disc.¹⁻⁶ However, despite the need to interpret these important findings for the clinician and to involve basic scientists more fully in the challenge of discogenic low back pain, to date there has been a lack of editorial reviews.⁷

By the 1960s, the innervation of the structures in the anterior part of the spinal canal was assumed to be well defined.⁷⁻¹³ It was agreed that sinuvertebral nerves arose bilaterally and segmentally, each formed by a fine sympathetic branch, usually arising from the grey ramus communicans, and a fine sensory spinal branch from the ventral ramus. These conjoined sinuvertebral nerves re-entered the vertebral canal through each intervertebral foramen to lie anterior to the nerve root in association with the segmental vessels.^{8,11,13} The sympathetic fibres were considered as vaso-motor efferents and the sensory fibres as proprioceptive and nociceptive.^{10,11,13} Branches were traced to the posterior longitudinal ligament,¹³ to the outer layers of the annulus fibrosus,^{10,13} and to the anterior dura.¹² Some nerves were perivascular, but others were observed to run independently. Many were seen to have a fine diameter suggesting A δ and/or C fibres, again

consistent with pain mediation.^{10,11,13} Most authors concluded that the lumbar sinuvertebral nerves had up to three segmental levels of overlap, which might explain the poor localisation of low back pain.^{7,8,12} Malinsky¹⁰ demonstrated a variety of free nerve endings and some button-like terminals in the outer few layers of the lumbar annulus and noted partially and fully encapsulated mechanoreceptors confined to the annular surface. They were found to increase in number and complexity with fetal and infantile growth. These observations were made with great precision, a difficult achievement using non-specific silver stains. Jackson et al,¹³ who were the first to recommend nerve-specific cholinesterase staining for the lumbar spine, corroborated Malinsky's¹⁰ findings.

In the early 1980s Bogduk, Tynan and Wilson¹⁴ and Bogduk¹⁵ clarified the innervation of the outer layers of the annulus. By microdissection and histology, they found that the posterior part of the human disc was supplied not only from the sinuvertebral nerve but also received direct branches in its posterolateral aspect from the ramus communicans or the ventral ramus. Branches from the grey ramus communicans also supplied the lateral aspect of the disc. Anterior discal nerves were observed to arise solely from the sympathetic

■ M. A. Edgar, MChir, FRCS, Retired Orthopaedic Surgeon, Emeritus Reader in Surgery UCL, Fellow of UCLH Emmanuel Kaye House, 37a Devonshire Street, London W1G 6QA, UK.

Correspondence should be sent to Mr M. A. Edgar at; e-mail: mae-hornbeams@googlemail.com

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plexus surrounding the anterior longitudinal ligament,⁵ suggesting a new concept whereby part of the disc might be supplied from sympathetic fibres only. This raised the question as to whether these nerves contained not only postganglionic efferent fibres but also sympathetic afferents conveying pain impulses.

In 1990 the debate continued with two independent studies of whole-mount lumbar spinal specimens from the human fetus^{16,17} and the rat^{18,19} using acetylcholinesterase histochemistry, which stains both adrenergic and cholinergic fibres. Groen et al^{16,17} confirmed earlier findings, but observed that human lumbar sinuvertebral nerves were found to arise only from the grey ramus communicans without any direct contribution from the spinal nerves, suggesting a totally sympathetic innervation. In contrast, Kojima et al^{18,20} concluded that the rat had a dual sensory pathway. The sinuvertebral nerves were observed to divide around the posterior longitudinal ligament into superficial and deep networks, the latter being segmental, confined to the intervertebral part of the ligament and supplying the posterior annulus. Resection of the dorsal root ganglia resulted in the destruction of most of these deep nerves segmentally, but had only a small effect on the superficial network, which was found to be non-segmental and extending over several levels, with each nerve dividing into ascending and descending branches, suggesting that they were predominantly sympathetic. Another centre in Japan repeated the study by Kojima et al,²⁰ but performed lumbar sympathectomy¹⁹ instead of resection of the dorsal root ganglia. The effect was variable, but it was noted that over 90% of the sensory innervation to the posterior annulus of the lumbosacral discs of the rat disappeared, indicating a major sympathetic component and thus favouring Groen's results.

With the advent of immunohistochemistry,^{21,22} the preparation of stains immunoreactive to neuropeptides and other neurotransmitters not only enabled nerves to be identified using general nerve markers, such as neurofilament stain NF200^{5,21} or protein gene product PGP-9.5,^{23,24} but also to be classified further according to function. For example, substance P^{25,26} and calcitonin gene-related peptide^{22,23,27,28} immunoreactive-staining identified nociceptive nerves, tyrosine hydroxylase immunoreactive-staining²⁹ distinguished sympathetic fibres, and vasoactive intestinal polypeptide immunoreactive-staining^{5,23,29} was thought to select postganglionic sympathetic efferents.

Using calcitonin gene-related peptide and tyrosine hydroxylase immunoreactive-staining, Imai, Hukuda and Maeda³⁰ confirmed Kojima's observations of a superficial and deep posterior longitudinal ligament nerve plexus in the rat.^{18,20} Calcitonin gene-related peptide fibres were seen in both plexuses, whereas tyrosine hydroxylase-immunoreactive fibres were observed only in the superficial plexus, suggesting a mainly sympathetic supply. Rats which had undergone resection of their dorsal root ganglia showed major loss of neurons, not only sequentially in the deep

plexus, but also more widely among the superficial plexuses, particularly in the lower lumbar region. Although supporting the dual pattern theory of sensory innervation, they commented on the predominance of the sympathetic supply in the superficial plexus. The close association of the postganglionic efferent and sympathetic afferent (nociceptive) fibres reflected a similar pattern to that seen in certain enteric organs,^{30,31} leading them to suggest that "low back pain is a kind of visceral pain". This hypothesis is considered in more detail later.

Over the last decade or so, besides immunoreactive staining, other developments involving experimental neuroanatomy and neuron transport markers have led to further hypotheses on the nature of discogenic pain. These areas of research are best considered under three headings.

The sensory pathways from the annulus and the posterior longitudinal ligament

The unravelling of 'the wiring diagram' of sensation and pain pathways from the lumbar disc and the posterior longitudinal ligament to the dorsal root ganglion and upwards through the spinal tracts has been a challenge beyond the scope of micro-dissection and histological sections alone. The intricate experimental studies which have further elucidated these pathways were initially performed in the anatomical and experimental orthopaedic departments in Chiba^{2,3,19,28,32-35} and later in other Japanese centres,^{36,37} along with international collaboration.^{31,38}

Using two different retrograde transport markers, horseradish peroxidase crystals and cholera toxin B, which travel from labelled nerve endings to the neuron body, the Chiba team injected the anterior L5-6 discs of a series of rats and 48 hours later examined all the lumbar dorsal root ganglia histologically. Labelled neurons were only found in dorsal root ganglia at the L1-2 level.³² As a result, the authors hypothesised that afferent nerve fibres from the annulus pass into the sympathetic chain to re-enter the sensory nerve roots at L1 and L2, the levels with white rami communicantes. Contemporaneous reports of local anaesthetic blocks to sympathetic ganglia at the L2 level providing relief in patients with discogenic low back pain,¹ and experimental studies in rats demonstrating a raised pain threshold after sympathectomy,³⁶ supported these findings. Parallel experimental studies suggested that the lower lumbar facet joints have a similar sensory pathway.³³

However, this initial neuron-transport research from Chiba was concerned only with the anterior annulus, which is known from the findings of Bogduk et al¹⁴ and Bogduk¹⁵ to be supplied predominantly or solely by sympathetic nerves. Therefore, some doubt was cast as to whether these results were applicable to the all-important innervation of the human posterior annulus, the main site of lumbar discogenic pain. Also, the clinical study of L2 sympathetic blocks¹ is open to the criticism of being highly subjective.

Next, by using calcitonin gene-related peptide-immunoreactive staining for nociceptive sensory afferents

and vasoactive intestinal polypeptide-immunoreactive staining for postganglionic sympathetic fibres, again in rat lumbar spines, the Chiba group observed both these groups of nerve fibres in the posterior longitudinal ligament and superficial posterior annulus.² They traced them through the superficial or deep posterior longitudinal ligament plexuses to the ramus communicans passing either directly or via the sinuvertebral nerve.² They, like Groen et al^{16,17} found no connection between these labelled neurons and the ventral rami of the spinal nerve. The vasoactive intestinal polypeptide immunoreactive fibres were both perivascular, suggesting an efferent vasomotor role, and independent of blood vessels indicating some other regulatory function.² In order to trace these pathways further, the Chiba team ingeniously placed fluorogold crystals, another retrograde neuron transport marker, in the posterior part of the L5-6 disc of sympathectomised and control groups of rats.^{28,35} Their findings supported a dual sensory pathway, one being unsegmented via the sympathetic chain, predominantly to the L1-2 dorsal root ganglia, and the other being segmental via the sinuvertebral nerves and the rami communicantes into the lower lumbar dorsal root ganglia. Again, this dual pattern fitted with the superficial and deep posterior longitudinal ligament plexuses, respectively.^{18,20} Finally, by using DiI, a reverse or antegrade neuron transport marker, to label the dorsal root ganglia in the upper lumbar region,³ the same group found the marker in nerve endings both within the upper lumbar discs, thought to be transported via the segmental sinuvertebral nerves, and also within the lower lumbar discs, thought to be transported by sympathetic fibres via the sympathetic trunk.

The concern that many of these results had not been fully corroborated was dispelled with an important collaborative study.⁶ Using an experimental method developed earlier,^{37,38} Cavanaugh et al³⁸ stimulated the posterior surface of the L5-6 discs of a series of rats both with an electrical current and mechanically, after inducing inflammation. Recording electrodes were placed on the L2 rootlets cephalad to the L2 dorsal root ganglia, which had been dissected to be the only connection via the ramus communicans to the sympathetic trunk. Their positive findings prompted the authors to conclude that "this experiment has confirmed the presence of a clear nociceptive pathway of sympathetic afferent discharge from the dorsal aspect of the lower lumbar intervertebral discs to the dorsal roots of L2" in rats. They also joined the body of opinion which hypothesised that lumbar discogenic pain is indeed a variety of visceral pain.

The experimental work of Indahl et al^{39,40} in pigs must also be recognised. Electrical stimulation to the lateral aspect of the annulus of an upper lumbar disc produced multilevel bilateral motor unit action potentials in the lumbar multifidus musculature. Conversely, electrical stimulus to an adjacent facet joint caused only a localised, unilateral response. It is reasonable to propose that the annular stimulus was transmitted *via* the widespread non-segmental sympathetic afferents. The pattern of response suggests a

spinal reflex through internuncial neurons to the anterior horn cells. Distension of the adjacent facet joint with saline depressed the motor unit action potentials,⁴⁰ thought to be due to the effect of muscle spindles in the facet capsule and possibly in the annulus if the posture of the whole motion segment was altered. Therefore, an interesting postural mechanism has been identified which, with induced muscle spasm, could have implications for pain.

Pattern of nerves and nerve endings in the normal and the degenerate disc

Even with the unreliable penetration of silver stains used in early studies, it has always been agreed that the normal nucleus pulposus and inner annular zones are devoid of nerves. However, early opinions were divided as to whether the outer annulus was innervated^{10,11,13} or not.^{7,9} Since then, authors have generally agreed with Malinsky's classic observations that the superficial layers of the normal annulus have sensory nerve endings,^{23,24,38,41,42} the depth of neural penetration in the human annulus being about 3 mm²⁵ and involving the three outer lamellae.²⁴ These nerves are small in diameter, probably Aδ- or C-type fibres,²⁷ and are relatively sparse compared with the profuse network on the disc surface and in the posterior longitudinal ligament and peridiscal tissues.^{19,22,24}

In degenerative discs, nerves had been observed in the outer half of the annulus using the conventional silver stain,⁴³ but with more specific acetylcholinesterase and immunoreactive staining, nerve fibres have been seen to extend deeper,^{25,44} even up to the inner third in 50% of painful degenerative discs.²⁷ Many of these nerves were observed in a perivascular position, suggesting that they arise from granulation tissue growing into the degenerative disc, neo-innervation.⁴⁴ One editorial comment⁴⁵ pointed out that the value of some of these studies was limited by the specimens of degenerative disc having been harvested during anterior lumbar fusion and hence limited to the anterior disc only,^{23,25-27,43,44} whereas the major radial crevices that contain granulation tissue mainly occur posteriorly.⁴⁶

A new study from Beijing⁵ examined posterior degenerative disc material removed during wide posterior disc excision and posterior fusion. The histological specimens were allegedly chosen to contain the degenerative annular tears identified on the pre-operative CT discography, which is a difficult task. Some substance P-immunoreactive and vasoactive intestinal polypeptide-immunoreactive stained nerve fibres were observed in the granulation tissue, and these appeared to extend deep into the disc. The histology of the nerves is consistent with a nociceptive function. Other recent studies^{42,47} have shown that the lumbar vertebral end-plate, particularly in its central area adjacent to the nucleus pulposus, is supplied with a neural pattern similar to that of the outer annulus.

Malinsky's original findings¹⁰ on the pattern of nerve endings have been confirmed recently in normal and degen-

erative spines.^{23,41,43} Roberts et al²³ looked specifically at mechanoreceptors in both scoliotic lumbar discs, from pain-free patients, and degenerative lumbar discs from patients with back pain, using a variety of immunoreactive nerve markers. Although the specimens were limited to anterior disc sections removed surgically, 50% of those from the low back pain group demonstrated mechanoreceptors, compared with only 15% in the scoliosis patients. This suggests proliferation in response to the pathology of degeneration. Golgi tendon organs type III and Ruffini endings type I have also been observed. Golgi end-organs are thought to have a nociceptive as well as a mechanoreceptor function.⁴⁸ The former could be mediated by increased muscle tone, consistent with the findings of Indahl et al.^{39,40}

The nature of discogenic pain

Mechanical stimuli which are normally innocuous to disc nociceptors can, in certain circumstances, generate an amplified response which has been termed 'peripheral sensitisation'.⁴⁹ This may explain why some degenerative discs are painful and others not.⁵⁰ Exposed nuclear material is known to irritate the spinal nerve root and probably also the sinuvertebral nerve endings.⁵⁰⁻⁵² Inflammation of joints causes mechanically insensitive afferents to become active through the secretion of pro-inflammatory mediators.⁵³ In degenerative disc disease the inflammatory granulation tissue present in annular tears and associated with invading nerves,⁵ behaves in a similar way.^{4,49,54} This peripheral sensitisation has been confirmed both clinically⁵⁵ and experimentally,⁶ and may not only affect type IV nociceptive free endings but also type III mechanoreceptors.^{23,26} Increased numbers of mechanoreceptors²³ and calcitonin gene-related peptide-immunoreactive neurons have been noted in discs from patients with chronic discogenic pain.^{32,47}

However, there is a more subtle method of 'peripheral sensitisation' relevant to chronic degenerative disc pain. The authors of a number of recent papers suggest that the sensory nerve supply of the disc is similar to that of certain enteric structures and represents a form of visceral pain.^{6,30,34} It is established that a high proportion of nociceptive nerve fibres arising from the annulus of the lower lumbar discs pass through the sympathetic trunks in a non-segmental manner and may be regarded as sympathetic sensory afferents. The peripheral endings of these nerves reveal a preponderance of calcitonin gene-related peptide-immunoreactive fibres,^{28,32} also seen in enteric structures.⁵⁶ Many of the peripheral branches of these nerves are seen close to sympathetic postganglionic efferent fibres, probably fulfilling a neuroregulatory function.^{30,31} There is growing evidence that these pain receptors are peripherally sensitised by the activity of sympathetic efferents,^{33,57,58} and that, conversely, experimental sympathectomy reduces this pain response.^{57,59} It is suggested that these nociceptive afferents behave similarly to sympathetic afferents in enteric or visceral structures, which may initiate a pain

impulse in response to ischaemia, pressure changes (mechanoreceptors) or inflammatory irritation.⁶⁰ Apart from the first, which is speculative, the other two are clearly relevant to spinal pain.⁴

The visceral pain concept also opens the door to the possibility of 'central sensitisation' of the descending autonomic nerves as a result of 'stress' which may lower the threshold of visceral afferents, adding to the complexity of chronic discogenic pain, in parallel with the concept of psychosomatic abdominal pain.^{57,60}

Local spinal reflex mechanisms can also affect the stimulatory response.^{40,41} Similarly, our understanding of the effect of the dorsal root ganglion satellite cells on the mediation of pain is just beginning.^{61,62}

Mooney⁶³ hypothesised that "there is something unique about the nerves related to the spine and the spinal canal which makes the source of pain different from the rest of the musculoskeletal parts of the body". Could the answer be that the disc, unlike other joints, is uniquely provided with a predominantly visceral-type of nerve supply?

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