Neural connection between the ventral portion of the lumbar intervertebral disc and the groin skin

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This study was designed to investigate neural mechanisms of referred pain in lumbar intervertebral disc lesions. Patients with a degenerative disc in lower lumbar segments occasionally complain of groin pain, which cannot be explained anatomically as having a radicular origin.

In rats pretreated with intravenous application of Evans blue dye, the dye extravasation appeared in the groin skin after application of capsaicin to the ventral portion of the L5–6 intervertebral disc. This response occurred even in rats with a sectioned L-5 spinal nerve and sympathetic trunks, but did not occur in rats with a sectioned genitofemoral nerve. Capsaicin topically applied to the sciatic nerve did not cause dye extravasation in the hindpaw. Therefore, groin dye extravasation was not due to a direct effect of capsaicin but, rather, presumably was caused by an “antidromic axon reflex” of dichotomizing C fibers or to a segmental sympathetic reflex causing vascular permeability.

The present results indicate that the ventral portion of the lumbar discs is neurally connected to the groin skin via the upper (L-2) lumbar spinal nerves in rats. Groin pain coincident with low-back pain may be explained as referred pain, indicating that a lesion is present in the ventral portion of the lumbar intervertebral disc space.

KEY WORDS • lumbar intervertebral disc • referred pain • groin • innervation • C fiber • capsaicin

Lesions of lumbar intervertebral discs are the most frequent causes of low-back pain. However, diagnosis of the causative disc is difficult because neurological examinations are not helpful in assessing patients without radiculopathy and because radiological abnormalities do not necessarily indicate pain origin. Even today, symptomatic discs can be determined only by using a pain provocation test during discography. However, discography is rarely indicated for patients who only exhibit low-back pain because their complaints are generally treated conservatively. Thus, it is clinically valuable to propose theories that differentiate causative discs based on patients’ symptoms and signs.

Pain generated by lumbar disc lesions is not localized at the causative disc; rather, it extends downward to the buttocks and lower limbs. Therefore, this pain is thought to be composed of original discogenic pain and pain referred to low-back structures (local referred pain) and lower limbs (referred limb pain), as stated by Jinkins, et al. If referred pain is localized in a particular region, depending on the lesioned disc, it may be possible to locate the disc according to the characteristics of the referred pain.

Investigations of referred pain have primarily focused on visceral pain. A diseased viscus can be diagnosed relatively accurately based on laboratory and radiological data, and pain apart from the viscus can be regarded as referred pain. In the case of the lumbar disc, however, diagnosis is difficult. Moreover, a degenerative disc frequently produces a herniation that compresses nerve roots and leads to radicular pain. Because radicular and referred pain mimic each other in nature and distribution, there is a tendency to regard lower-limb pain as having a radicular origin. Interestingly, however, patients with a degenerative disc in the lower lumbar segments occasionally complain of groin pain. This groin pain cannot have a radicular origin because the groin skin is in the dermatome area of the upper lumbar spine (L-1 or L-2). Thus, for lumbar disc lesions, it is necessary to map the referred pain area before an investigation of its mechanism can be undertaken.

Histologically, free nerve endings have been found in the longitudinal ligaments and outer layers of the annulus fibrosus. Substance P or calcitonin gene–related peptide immunoreactive nerves have been demonstrated in lumbar discs. Mechanical stimulation of lumbar discs elicits C-fiber discharges in nerve roots. These results suggest the presence of afferent C fibers, which are thought to transmit pain in lumbar discs.

Dichotomizing primary afferent C fibers, which innervate both a visceral organ and a somatic structure, have been demonstrated and addressed as a cause of referred pain; it is speculated that C-fiber impulses from a visceral organ are antidromically transmitted to induce “neurogenic inflammation” in the referred skin area.
ternatively, there is another hypothesis: that the thermal increase in the referred pain area is the result of reflex vasodilation. Based on these hypotheses, we speculated that if such neural structures also exist in the lumbar disc, stimulation of their nerve endings may result in vascular responses in the area of referred pain.

Cutaneous neurogenic plasma extravasation can be visualized by means of intravenous injections of Evans blue dye in rats. Using this technique, we investigated skin color changes following application of capsaicin, a specific chemical stimulant of C fibers, to the lumbar disc of rats. A brief outline of the experiment has been reported in a previous paper. In the present study, we also investigated the effect of capsaicin on peripheral nerves.

Materials and Methods

Male Sprague–Dawley rats, weighing 250 to 350 g, were anesthetized by an intraperitoneal administration of sodium pentobarbital (40 mg/kg). The rat trachea was cannulated to maintain spontaneous respiration. The hair of the caudal half of the animal was completely shaved and removed with a commercially available depilatory. Rectal temperature was maintained between 37˚C and 38˚C. Rats were laid supine and attached to an operating table with vinyl tapes surrounding the chest and upper limbs. The back, abdomen, and lower limbs were not taped to avoid nonrelevant dye extravasation into the skin. Capsaicin (Wako Pure Chemical, Osaka, Japan) was dissolved in vehicle (10% ethanol and 10% Tween 80 (weight/weight) in physiological saline to a concentration of 1% (weight/volume)). Evans blue dye was dissolved in physiological saline and injected into the right cephalic vein (30 mg/kg) when required.

Experiment 1: Application of Capsaicin to the L5–6 Disc Space

The ventral portion of the L5–6 disc space was exposed between the aorta and the left psoas major muscle via a ventral approach using a dissection microscope. The muscle and overlying left genitofemoral nerve were retracted laterally. Ten minutes following this procedure, Evans blue dye was injected into the animal. After 10 minutes, in 26 rats, 1 ml of capsaicin, dissolved in vehicle (10 µg at dose), was injected into the annulus fibrosus of the L5–6 disc space 1 mm left of the midsagittal line using a 10-µl Hamilton microsyringe. In 19 other rats, 1 ml of vehicle was injected into the same point of the disc. Skin color changes were observed after 30 minutes.

To determine the neural pathway, nerves surrounding the disc were sectioned using bipolar cautery 30 minutes before application of capsaicin to the L5–6 disc space. The left genitofemoral nerve (from 16 animals) and the bilateral sympathetic trunks (from 12 animals) were sectioned at the L-4 level. The L-5 spinal nerve was sectioned just distal to the L-5 dorsal root ganglion (in nine animals). The left L-2 ventral and dorsal nerve roots were sectioned in the spinal canal after laminectomy (six animals) (Fig. 1).

Experiment 2: The Effect of Capsaicin on Peripheral Nerve Fibers

The aim of this experiment was to determine whether a direct application of capsaicin to peripheral nerve fibers results in dye (plasma) extravasation in the corresponding skin region. The right and left sciatic nerves were exposed ventrally at the midthigh while the rat was supine. Ten minutes after this procedure, Evans blue dye was intravenously administered.

Group A (16 Animals). Using a 1-ml tuberculin syringe with a 27-gauge needle, 10 µl of capsaicin solution and vehicle were gently administered under the epineurium of the right and left sciatic nerves, respectively. Skin color changes were observed for 30 minutes.

Group B (14 Animals). Similarly, 10 µl of capsaicin solution and vehicle were applied to the right and left sciatic nerves, respectively. Ten minutes after application, the nerves were sectioned 1 cm proximal to the application site, and the distal stump was elec-
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Fig. 3. Schematic drawings showing the location of blue spots of dye extravasation (dots). The shaded area indicates the genitofemoral nerve area as determined by dye extravasation after electrical stimulation of the nerve.

Experiment 1: Application of Capsaicin to the L5–6 Disc Space

Eighteen of the 19 rats that received vehicle did not show any skin color changes; the remaining rat showed a few small blue spots in the groin skin caused by dye extravasation. In contrast, 22 of the 26 rats that received capsaicin showed blue spots in the ipsilateral groin skin. The number, size, and distribution of these blue spots differed considerably among animals (Figs. 2 and 3). The blue spots appeared in the innervation area of the genitofemoral nerve; this area was determined in other rats by dye extravasation following electrical stimulation of the nerve under the same conditions as in Experiment 2. In nine of the 22 rats that exhibited groin dye extravasation, a few small blue spots also appeared in the base of the hindlimb (Fig. 3). The remaining four rats did not show any changes in skin color.

Of the 16 rats who had a sectioned genitofemoral nerve, 13 showed no skin color changes; of the nine rats with a sectioned L-5 spinal nerve, five showed groin dye extravasation; of the 12 rats whose sympathetic trunks were sectioned, 10 showed groin dye extravasation; and of the six rats whose L-2 nerve roots were sectioned, two showed blue spots in the groin, but the number and size of spots were markedly reduced. Data are summarized in Table 1.

Fig. 4. Photographs displaying rat hindpaw soles. A: Group A. Blue spots and color changes do not appear either in the right, capsaicin-treated side or in the left, vehicle-treated side. B: Group B. A blue-stained area appears after electrical stimulation of the sciatic nerve in the left, vehicle-treated side. In contrast, dye extravasation is completely inhibited in the right, capsaicin-treated side.

Experiment 2: Effect of Capsaicin on the Sciatic Nerve

Group A. The hindpaws did not show any blue spots or color changes in either the capsaicin- or vehicle-treated sides after application (Fig. 4). It should be noted that blue spots appeared in the lateral side of the hindlimb on the capsaicin-treated side in nine rats. The Evans blue dye content in the sole tissue in the capsaicin-treated side and in the vehicle-treated side was not statistically different (Fig. 5).

Group B. As in Group A, no rats showed any skin color changes in the hindpaw after application in either the capsaicin- or vehicle-treated side. Electrical stimulation of the distal stump of the sciatic nerves caused marked dye extravasation in the vehicle-treated side, whereas it was
almost completely inhibited in the capsaicin-treated side (Fig. 5). The Evans blue dye content was significantly higher in the vehicle-treated side than in the capsaicin-treated side (Fig. 5).

Discussion

Effects of Capsaicin on Nerve Fibers

The skin color changes exhibited after capsaicin was applied to the L5–6 disc space (Experiment 1) seem to be induced by stimulation of nerve terminals existing in the annulus fibrosus of the discs. However, because the annulus fibrosus is a fibrous cartilage, the capsaicin solution may overflow from the discs and may directly affect the surrounding nerves, resulting in plasma extravasation.

It has been reported that when topically applied to rat peripheral nerves capsaicin causes: 1) a conduction block in C fibers,3,2) depolarization of C fibers,24 3) interception of axonoplasmic transportation of substance P,11 4) depletion of substance P in the skin and spinal cord,12 and 5) local hyperemia of the nerve.42 However, to date it has not been examined whether topical application of capsaicin to the peripheral nerve elicits plasma extravasation in the corresponding skin. Kenins22 explained that capsaicin acts at receptors, not axons.

In Experiment 1, it was demonstrated that direct application of capsaicin to the sciatic nerve did not cause plasma extravasation, although it blocked C-fiber conduction. This implies that capsaicin damages C fibers in the peripheral nerve without causing ectopic firing therein. Therefore, we concluded that the dye extravasation seen in Experiment 1 was due to some reflexlike mechanisms.

“Efferent” Pathways of Groin Dye Extravasation

In 22 of 26 rats groin dye extravasation appeared in the innervation area of the left genitofemoral nerve, whereas in 13 of 16 rats in which the nerve had been cut it did not appear. These results suggest that the “efferent” neural path of the response follows the genitofemoral nerve. The small blue spots seen in the groin of two rats with a sectioned genitofemoral nerve may have been due to injury discharges from the sectioned stump.

Blue spots also appeared in dermatomes of the L5–S1 region29 in the hindlimb. The efferent path of this response seems to be along spinal nerve from L-5 to S-1. Capsaicin applied to the L5–6 disc space may have infiltrated dorsally around the disc into the L-5 dorsal root ganglion. It is reported that capsaicin acts on dorsal root ganglia to generate ectopic firing.40 Therefore, it cannot be denied that dye extravasation in the hindlimb is due to the direct effect of capsaicin. Thus, hereafter we will consider exclusively the neural pathways for the “groin response” on the basis of groin dye extravasation after application of capsaicin to the L5–6 disc space.

Innervation of the Ventral Portion of Lumbar Discs

Some physiological investigations suggest that each lumbar disc is innervated segmentally by its corresponding spinal nerve.13,32 In contrast, anatomical studies have revealed that prevertebral sympathetic trunks and ramus communicantes supply nerves to the lumbar disc.6,16,32 Moreover, the role of the sympathetic nerves in low-back pain has been reported clinically10 and experimentally.14

Recently, in our histological investigations of the innervation of the rat L5–6 disc space we observed the following: 1) horseradish peroxidase applied to the ventral portion of the disc was retrogradely transported exclusively to the L-1 and L-2 dorsal root ganglia;27 2) the nerve plexus on the dorsal portion of the disc was partially reduced after resection of bilateral prevertebral sympathetic trunks and was abolished after their total removal;28 3) immunohistochemically determined sensory fibers that originate from the posterior portion of the disc and join with the ramus communicantes were found (unpublished data). These results indicate that “sympathetic afferents,” which conceivably originate from L-1 or L-2 segments, innervate either the ventral or dorsal portions of the disc. They probably play a role in the “afferent” path of the present “groin response.”

TABLE 1

Areas of dye extravasation after application of capsaicin to the L5–6 disc space in rats

<table>
<thead>
<tr>
<th>Condition of Experimental Animal</th>
<th>Groin &amp; Hindlimb</th>
<th>Hindlimb Change</th>
</tr>
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<tbody>
<tr>
<td>without sectioning of surrounding nerves (26 animals)</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>after section of genitofemoral nerve (16 animals)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>L-5 spinal nerve (9 animals)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>sympathetic trunks (12 animals)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>L-2 nerve roots (6 animals)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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If the dorsal portion of the L5–6 disc space was innervated by sympathetic nerves multisegmentally, the innervation of the ventral portion may be this analog. This presumption may explain the present result that the “groin response” was still recognized in rats with sectioned sympathetic trunks. As we described in a previous paper, the somatic afferents in the psoas major muscle may be another candidate for the afferent path because nerves supplying the bone surface are generally derived from the muscle to which they attach.

Mechanisms of Groin Dye Extravasation

The “groin response” may be induced via dichotomizing capsaicin-sensitive sensory C fibers in the L-2 spinal nerve. The incidence of dichotomizing fibers ranges widely from 0.1% to 25% and differs considerably among subjects. This may explain the discrepancy of the “groin response” between animals. Some investigators, however, are skeptical about the role of dichotomizing fibers in the referred pain because such fibers are rare. Neurone plasma extravasation has been known to be mediated exclusively by sensory C fibers. However, the contribution of sympathetic efferents in cutaneous plasma extravasation has been addressed recently. The present result that the “groin response” was reduced in rats with sectioned L-2 nerve roots may suggest the contribution of a spinal vascular reflex through sympathetic efferents. Thus, either the “antidromic axon reflex” of dichotomizing C fibers or a sympathetic reflex seem to be candidates for the neural mechanism of the “groin response” (Fig. 6).

These neural mechanisms may have contributed to the dye extravasation in the lateral side of the hindlimb in Experiment 2. If the nervi nervorum of the sciatic nerve at the midthigh and the lateral cutaneous nerve of the hindlimb are connected by dichotomizing fibers or a sympathetic reflex, stimulation of the nervi nervorum with capsaicin may induce “referred” dye extravasation in the lateral side of the hindlimb.

Clinical Relevance

If the ventral portion of the human lumbar disc is connected to the groin skin by the same neural systems as in rats, the groin pain associated with low-back pain can be explained as reported, indicating the presence of lesions in the ventral portion of lumbar discs. Groin pain is a rare symptom in patients with low-back pain. This may be attributed to the well-known fact that lumbar disc lesions usually develop in the dorsal portion of the lower segments.

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