**Permeability of Injured and Intact Peripheral Nerves and Dorsal Root Ganglia**

Stephen E. Abram, M.D.,* Johnny Yi, B.A.,† Andreas Fuchs, M.D.,‡ Quinn H. Hogan, M.D.*

**Background:** Nerve injury that produces behavioral changes of allodynia and hyperalgesia in animals is associated with electrophysiologic changes in dorsal root ganglion (DRG) cells. The introduction of drugs into the DRG or the peripheral nerve that alter calcium, sodium, or potassium channel activity may be of therapeutic benefit after nerve injury. For this reason, the authors sought to determine whether drugs that do not ordinarily cross the blood–nerve barrier will enter the DRG after intravenous or regional injection and to determine whether nerve injury alters drug access to DRGs or peripheral nerves.

**Methods:** Both intact and spinal nerve-ligated rats were injected with sodium fluorescein by intravenous, intrathecal, peri-DRG, perisciatic, and epidural routes. DRG, sciatic nerve, and spinal cord tissues were harvested and frozen, and histologic sections were analyzed quantitatively for tissue fluorescence.

**Results:** In both intact and nerve-injured animals, fluorescein accumulated in DRGs after intravenous, peri-DRG, and epidural injection. There was accumulation in the proximal portion of the ganglion after intrathecal injection. Minimal amounts of fluorescein were found in the sciatic nerve in intact animals after intravenous or perineural injection, but substantial amounts were found in some nerve fascicles in nerve-injured animals after both intravenous and perineural injection. There was almost no fluorescein found in the spinal cord except after intrathecal administration.

**Conclusions:** In both intact and nerve-injured animals, fluorescein accumulates freely in the DRG after intravenous, epidural, or paravertebral injection. The sciatic nerve is relatively impermeable to fluorescein, but access by either systemic or regional injection is enhanced after nerve injury.

The dorsal root ganglion (DRG) has been identified as an important site of pathology in human and animal neurologic disease. Ca\(^{2+}\) currents and cytosolic Ca\(^{2+}\) levels in DRG cells are reduced after both chronic constriction injury and spinal nerve ligation (SNL) in rats.\(^1\) \(^5\) Sprouting and proliferation of sympathetic fibers within the DRG occurs after nerve injury.\(^4\) Activation of neuroimmune mechanisms with resulting release of proinflammatory cytokines, chemokines, and other neuromodulators has been implicated in the pathophysiology of painful radiculopathy after extrusion of the nucleus pulposus.\(^5\) There are many potential therapeutic interventions that may reduce the consequences of nerve or nerve root injury through effects on the DRG, such as drugs that block or reverse neuroimmune activation,\(^5\) \(^6\) that block the effect of proinflammatory mediators,\(^6\) or that modify the excitability of peripheral sensory neurons via modulation of Na\(^+\), Ca\(^{2+}\), or K\(^+\) channels.\(^2\)

Although some potentially therapeutic drugs cross the blood–nerve barrier when injected systemically or across nerve sheath or dural barriers when injected epidurally or perineurally, many agents, particularly hydrophilic drugs, are excluded. However, it has been shown that the DRG has different permeability characteristics than most neural structures. Substances that are excluded by vascular–nerve barriers from peripheral nerves, brain, and spinal cord readily penetrate the DRG\(^7\) and trigeminal ganglion\(^8\) when injected intravenously. Little is known about the permeability of the DRG to substances injected locally. In the experimental setting, drugs are injected intrathecally with the intention of delivery to the DRG,\(^9\) but there is little information validating the access to the DRG of drugs by this route. Horseradish peroxidase, a large molecule (\(44,000\) Da) with a net positive charge, has been shown to gain access to the sacral DRGs but not to the ventral root when injected epidurally in pigs.\(^10\) We could find no data regarding access to the DRG of hydrophilic drugs injected in the paravertebral space adjacent to the DRG.

After nerve injury, nerve sheath and blood–nerve barriers become more permeable,\(^11\) \(^12\) but little is known about the effects of nerve injury on drug access to the DRG. Nerve injury may increase DRG permeability because of damage to epineural, perineural, or vascular membranes or reduce permeability because of fibrosis and scar formation. Given the potential benefits of administering drugs that target the DRG, we examined the access of a hydrophilic marker to the DRG when administered by several routes in both intact and nerve-injured animals. In addition, we sought to determine whether injury affects drug permeability of the adjacent sciatic nerve, which would ordinarily not be permeable to hydrophilic agents by either intravenous or local injection.

Sodium fluorescein was selected as the most appropriate tracer for examining access to the DRG. It is nontoxic\(^13\) and thus should not alter tissue barriers. It converts nearly all absorbed light to fluorescent light, so that it can be detected at very low tissue concentrations.\(^14\) Approximately 20% of the injected tracer remains unbound,\(^14\) and it has the diffusion characteristics of a relatively small molecule (molecular weight [MW] \(376\)). Like many therapeutic agents, it is a weak acid (pKa = 6.5). Most importantly, it has been shown not to cross normal blood–brain and blood–nerve barriers,\(^8\) and in—

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* Professor, Department of Anesthesiology. † Medical Student, Medical College of Wisconsin. ‡ Staff Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, Medical University of Graz, Graz, Austria.

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Address correspondence to Dr. Abram: Department of Anesthesiology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, P. O. Box 26099, Milwaukee, Wisconsin 53226-3596. sabram@mcw.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.
jection adjacent to healthy peripheral nerves produces little to no spread into the endoneurium.\textsuperscript{8}

From information that is available regarding access of hydrophilic drugs to peripheral nerves and DRG, we proposed the following hypotheses:

1. Substantial amounts of fluorescein would be seen in the DRGs after intravenous, intrathecal, epidural, and peri-DRG administration.
2. Spinal nerve ligation injury would not substantially change entry of fluorescein into the DRG.
3. There would be minimal uptake of fluorescein into the intact sciatic nerve after either intravenous or perineural injection.
4. Spinal nerve ligation injury would result in some increase in access of fluorescein into the sciatic nerve after both intravenous and perineural injection.

It is the aim of this study to test these hypotheses.

Materials and Methods

Studies were performed on male Sprague-Dawley rats (250–350 g) obtained from Charles River Laboratories, Inc. (Wilmington, MA) after approval from the Medical College of Wisconsin Animal Resource Center (Milwaukee, Wisconsin).

Spinal Nerve Ligation
Spinal nerve ligation was performed during halothane anesthesia using the method previously described by Kim and Chung.\textsuperscript{15} After exposure of the right paravertebral tissues, the sixth lumbar transverse process was resected, and the L5 and L6 spinal nerves (ventral rami) were ligated with 6–0 silk suture and cut distal to the ligature. In contrast to the procedure described originally, paraspinal muscles and the adjacent articular process were not removed. Control animals were either exposed to no surgery or received only anesthesia and skin incision. After surgery, animals were returned to the animal colony, where they were kept in individual cages under normal housing conditions. Fluorescein injections were performed 2–3 weeks after nerve ligation surgery. Doses and timing of fluorescein injections were based on results of previously published studies as well as on pilot studies for this project.

Intravenous Injection
After induction of halothane anesthesia, the femoral vein was cannulated with a PE-50 catheter, and 10 mg sodium fluorescein in 2 ml normal saline was injected over 30 s. Inhalation anesthesia was maintained for 30 min, at which time the chest was opened and the aorta was perfused with phosphate buffer until venous blood appeared clear. Perfusion was continued with 20 ml paraformaldehyde, 4%, after which the right L4 and L5 and left L5 DRGs, spinal cord, and right and left proximal and distal sciatic nerve segments were harvested. Tissues were frozen by immersion in 2-isobutane cooled in dry ice.

Intrathecal Injection
Intrathecal injection was performed as described by Yaksh and Rudy.\textsuperscript{16} Briefly, a PE-10 catheter was introduced during halothane anesthesia via the atlanto-occipital membrane and advanced 12 cm, the distance found to reach the level of the L5 foramen. Sodium fluorescein, 50 \(\mu\)g in 10 \(\mu\)l normal saline, was injected via the catheter, which was then removed. Anesthesia was maintained for an additional 30 min, at which time intracardiac perfusion was performed as described above. The right L4 and L5 DRGs, the left L5 DRG, and the lumbar spinal cord were harvested and frozen.

Sciatic Nerve Injection
Animals were anesthetized with halothane, and the sciatic nerves were exposed in the lumbosacral paravertebral tissues by splitting the sacrum laterally and gently spreading the surrounding muscles. Sodium fluorescein, 500 \(\mu\)g in 100 \(\mu\)l normal saline, was injected under the epineurium with care to avoid entry into the mesoneurium, at a site just distal to the L6 nerve root. In animals that had previously undergone SNL, ligation, both the right (ligated) and left sides were injected. In control animals, only the right sciatic nerve was injected. After surrounding tissues were reapproximated, the animals remained anesthetized for 30 min. After aortic perfusion, sections of the nerve were removed and frozen. A segment of nerve approximately 1 cm in length was harvested.

Dorsal Root Ganglion Injection
Animals were anesthetized with halothane, and the right lumbar paravertebral tissues were exposed in a manner similar to that used to perform the spinal nerve ligation. Muscle tissue was gently dissected away until the right L5 neural foramen could be identified. A blunt 30-gauge needle was advanced 5 mm into the foramen, and sodium fluorescein, 500 \(\mu\)g in 100 \(\mu\)l normal saline, was injected. After surrounding tissues were reapproximated, the animals remained anesthetized for 30 min. After aortic perfusion, the right L4 and L5 DRGs and the left L5 DRG were harvested and quickly frozen in cold 2-isobutane. During harvest, the spinal cord was exposed and viewed under ultraviolet illumination. Absence of spinal cord fluorescence was used to assure that there was no unintended intrathecal injection of the fluorescein.

Epidural Fluorescein Injection
Animals were anesthetized, and a small incision was made in the midline at the L6–S1 level. A small portion
of the L6 lamina was removed, exposing the underlying dura. A PE-10 catheter was advanced 1 cm cephalad in the epidural space, and fluorescein, 500 μg in 100 μl normal saline, was injected. The catheter was removed, and the overlying tissues were reapproximated. Anesthesia was maintained for an additional 30 min, at which time aortic perfusion was performed. The right L4 and L5 DRGs, the left L5 DRG, and the spinal cord were harvested and frozen. As the dura was opened, the cerebrospinal fluid was inspected to make sure that the fluorescein had not been injected intrathecally.

**Histologic Preparation and Fluorescent Imaging**

After harvest, tissues were embedded in tissue freezing medium (Triangle Biomedical Sciences, Durham, NC) and sliced at a thickness of 10 μm using a cryostat microtome. Tissues were mounted on glass slides and, after drying for 1 h, were covered with toluene mounting medium (Shur/Mount-Toluene Base; Electron Microscopy Sciences, Ft. Washington, PA) and a glass coverslip. Imaging was completed using fluorescence microscopy at 40× and 100× frames of each tissue slice. Fluorescence intensity was recorded at 515–555 nm wavelength with a cooled CE model 2.1.0 camera (Diagnostic Instruments, Inc., Sterling Heights, MI) using fixed acquisition parameters, including excitation intensity and acquisition time, to assure consistent recording of intensity. Signal intensity for areas of interest was determined as the average intensity of each pixel, which ranged from 0 to 256 for the 8-bit camera system and is expressed as arbitrary units. To avoid bias in selection of regions to scan, cellular (areas containing mainly cell somata) and axonal areas of neural tissue were identified and selected on bright field images before viewing the fluorescent images, and overlays of those areas were used for digital quantification of the fluorescent images (Sigma Scan; Systat Software, Inc., Port Richmond, CA). When comparing proximal versus distal areas of the DRGs, such selections were made in the distal half versus the proximal half of the DRG. Three or four separate regions were quantified for each sample and for each tissue type. Two to four SNL animals and two to four control animals were used for each site of fluorescein injection. If responses were consistent and satisfactory images were obtained, only two animals were used. For some groups, additional animals were used to obtain images of a quality suitable for publication. Neural tissues from an un.injected animal were imaged in a similar fashion. Because this revealed no autofluorescence, no background subtraction was used.

**Statistical Analysis**

Data are presented as mean ± SEM. In comparing fluorescence from two sites, a two-tailed, unpaired Student t test was used. When analyzing more than two sites, values were compared using either the one-way analysis of variance with Bonferroni multiple comparison test or the Kruskal-Wallis analysis of variance on ranks with Dunn multiple comparison test for nonparametric data. Differences were considered significant at P ≤ 0.05.

**Results**

**Intravenous Injection**

For control animals, there was substantial accumulation in the L4 and L5 DRGs, with the highest intensity of fluorescence seen in the portions of the DRG containing mainly cell somata (which we have termed “cellular”) followed by areas containing mainly axons (which we have termed “fiber”) (fig. 1). There was no significant
The difference between the L4 and L5 values for cellular or nerve fiber components, and these data were combined (fig. 2). The intensity in the sciatic nerve was significantly lower than that of the cellular or fiber portions of the DRGs (fig. 3), and the intensity in the cord was close to background intensity (fig. 4). Sciatic nerve fluorescence was significantly higher than spinal cord fluorescence.

For SNL animals (fig. 2), fluorescence was again seen in all DRGs examined. Accumulation in the cellular portions of all DRGs was higher than in the nerve fiber portions, as was seen in control animals. There was no significant difference in the amount of fluorescence between the right (injured side) L5 DRG and the right L4 or left L5 DRG. A conspicuous difference from control was seen in uptake of fluorescein into the sciatic nerve on the injured side. There was significantly greater fluorescence on the right than on the left side, which was very low. Some sections of the proximal sciatic nerve on the injured side showed nerve fascicles with very high fluorescence adjacent to fascicles with low levels (fig. 3). Fluorescence was higher in the proximal than the distal portion of the sciatic nerve on the injured side. As in control animals, spinal cord fluorescence was very low.

**Intrathecal Injection**

For control animals, high intensities were seen in both gray and white matter of the spinal cord. There was high-level fluorescence seen in the proximal portions of the DRGs with a clear gradient of accumulation of fluorescein from proximal to distal. There were no differences between the L4 and L5 DRG, so data from the two levels were combined for comparison of uptake into the proximal versus distal portions (fig. 5). There was a significant difference in fluorescence of the proximal cellular and fiber areas compared with the distal areas. Unlike intravenous injection, fluorescein delivered by intrathecal injection accumulated comparably in the cellular and fiber portions of the DRG. Spinal cord fluorescence was high and was comparable to that of the proximal portion of the DRG. There was no difference in uptake between the gray and white matter of the cord.

For SNL animals, similar patterns of uptake into the spinal cord and DRGs were seen (fig. 5). There was significantly more fluorescein accumulation in the proximal portions of the DRGs than in the distal portions (fig. 1). In these animals, there was somewhat more fluorescence accumulation in the cellular areas than in the nerve.
fiber areas of the DRGs. Uptake into the spinal cord was high and was comparable to uptake into the cellular areas of the proximal portions of the ganglia (fig. 4). Again, there was no difference in fluorescein accumulation between gray and white matter of the cord.

**Sciatic Nerve Injection**

For control animals, a relatively low uptake of fluorescein into the right sciatic nerve (9.7 ± 3.6) was observed (fig. 3). For SNL animals, there was significantly higher uptake into the nerve on the right (nerve-injured) side (38.6 ± 4.8 [mean ± SEM]) compared with the left (18.5 ± 3.8) \( (P < 0.01) \). The sciatic nerve on the left was similar to that of control animals in appearance, whereas the nerve on the right (injured) side showed areas of moderate intensity and areas of high intensity (fig. 3).

**Dorsal Root Ganglion Injection**

For control animals, one-way analysis of variance showed a significant difference in uptake comparing cellular areas from the right L5 DRG (injection site), the right L4 DRG, and the left L5 DRG \( (P < 0.0001) \). As expected, high uptake was seen in the right L5 DRG (fig. 1), and lower levels were observed in the ipsilateral L4 and contralateral L5 ganglia. Lower levels of fluorescein were seen in the fiber areas than in cellular areas, but again, the differences among the three ganglia were significant \( (P < 0.0001) \), and the same relation (right L5 > right L4 = left L5) was seen (fig. 6).

For SNL animals, the uptake into the target L5 DRG was somewhat lower than for control animals but was still fairly high. The right L5 levels were higher than the right L4 or the left L5 for cellular areas \( (P < 0.01, \) one-way analysis of variance) and for fiber areas \( (P < 0.01, \) one-way analysis of variance) (fig. 6).

**Epidural Injection**

For the control animals, there was fairly high uptake of fluorescein into the L4 and L5 DRG cellular areas with less accumulation in fiber areas (fig. 7). Unlike for intrathecal injections, the uptake appeared uniform from the proximal to the distal portion of the ganglion (fig. 1). There was some asymmetry of uptake from right to left for individual animals, but the combined differences were not significant at either the L4 or L5 level. As expected, spinal cord uptake was negligible.

For the SNL animals (fig. 7), there was again uniformity of uptake from the proximal to the distal regions of the ganglia, including the right L5 ganglion. Again, the highest concentrations were seen in the tissues surrounding the cell bodies (fig. 1E). As with the control animals, there was some right-to-left asymmetry in individual animals, but the overall differences were not significant at either the L4 or L5 level. There was no difference in uptake between the right (nerve-injured side) L5 and the right L4 DRGs, suggesting that injury had little or no influence on fluorescein accumulation in the injured ganglia. Again, spinal cord uptake was very low.
Discussion

This study indicates that fluorescein, which does not cross healthy blood–brain or blood–nerve barriers, can gain access to the DRG via several routes, including intravenous, intrathecal, epidural, and paravertebral injections, and that nerve injury does not appreciably affect fluorescein accumulation in the DRG. The most selective technique seems to be paravertebral injection, at the site of the targeted DRG. However, drug delivery by this route is not perfectly selective, because fluorescein passed via the epidural space to the contralateral and adjacent DRGs. Nevertheless, levels found at the adjacent ipsilateral DRG or at the corresponding contralateral DRG are less than half the levels of the target structure. Accumulation of drug in the spinal cord was seen only after intrathecal administration.

Access of fluorescein to the DRG after intravenous injection is related to the absence of tight junctions in the endothelium of vessels supplying this structure. Previous studies using Evans blue albumin also showed preferential accumulation of fluorescent material in the cell body–rich portion of the DRG. That study also demonstrated that the tight junction proteins claudin-I and occludin were detectable in the nerve fiber–rich areas of the DRG but not in the cell body–rich areas.

Our data regarding drug passage into various neural tissues after intravenous injections is similar to the results of most previous studies. In the control animals, there was high uptake into the DRGs, low uptake into the sciatic nerve, and almost no uptake into the cord. These data again indicate that the blood–nerve barrier is more complete for the central nervous system than for peripheral nerves and is minimal for sensory ganglia. Malmgren and Olsson showed essentially no fluorescence in the cerebral cortex after intravenous fluorescein in mice regardless of the dose or the time after injection. They showed low levels of fluorescein in the nerve trunks of sciatic and hypoglossal nerves, and somewhat higher levels in small peripheral nerve branches. In trigeminal ganglia, they showed high levels of fluorescence around cell bodies 5 min after injection. An hour after injection, there was fluorescence throughout the extracellular space, but it was still more intense near the cell bodies. Olsson found that labeled bovine serum albumin, injected intravenously in rats, accumulated in DRGs, with minimal endoneurial uptake into dorsal or ventral nerve roots or into the sciatic nerve.

It is likely that accumulation of fluorescein in the interstitial spaces of the DRG after epidural or peri-DRG injection occurs through simple diffusion. The membranes surrounding or within the DRG do not contain tight junctions seen in the perineurium of larger peripheral nerves. Although it is possible that the drug entered the DRG via penetrating arterial vessels, this seems unlikely. A light and electron microscopic study of the spread of epidurally injected horseradish peroxidase (MW 40,000) into the DRG showed a gradient through the cell layers of the ganglion capsule. At 5 min after injection, horseradish peroxidase was detected in the extracellular space just below the DRG capsule, with faint distribution in the central portions of the DRG. There was no horseradish peroxidase detected within the capillaries. We could find no explanation for the difference in fluorescein accumulation in the areas around the cell somata versus the axonal regions of the DRG. It is possible that the hydrophilic dye is excluded from hydrophobic areas even though there is no barrier to diffusion into these regions.

Uptake of fluorescein by the injured and adjacent DRGs after intravenous and peri-DRG injection in SNL animals seemed slightly lower than for control animals, although statistical comparison could not be made using our protocol. It is possible that the perineural inflammation and scarring reduced spread of the material to the capsule of the DRG in the injured animals. Another possibility is up-regulation of multidrug-resistant proteins. These are adenosine triphosphate–dependent transport proteins that have been shown to have increased expression after neurologic disease or injury and that can increase active transport out of neuronal tissues. If these mechanisms indeed limit accumulation of fluorescein in the DRG after injury, the effect is small, and accumulation in DRGs after injury is still substantial. No differences in fluorescein accumulation in DRGs between control and SNL animals or between the right L4 and L5 DRGs in SNL animals was seen after epidural injection, again suggesting that nerve injury has minimal effect.

The effect of proximal nerve injury on access of fluorescein to the peripheral sciatic nerve is, on the other hand, very clear. As expected, after both intravenous injection and perineural injection of the sciatic nerve in intact animals, there was minimal transfer of fluorescein into the individual nerve fascicles. This lack of entry into nerve tissue after local injection is due to a perineurial barrier composed of flat cells joined by tight junctions with basal laminae arranged in concentric layers around the fascicles. In SNL animals, with both intravenous and perisciatic injection, we were able to identify nerve fascicles with high fluorescein content and others that seemed similar to those of the intact animal (fig. 3). Although our technique did not allow identification of the origin of the fascicles that contained fluorescein, we assume that they originated from the transected L5 and L6 segments, because these changes were never seen in the absence of transection. The spinal nerves at both of these levels (as well as L4) provide contributions to the sciatic nerve in the rat. Although we could not assess the extent of the peripheral nerve permeability changes that occurred after SNL, some fascicles with high levels of fluorescein were seen in all of the SNL animals examined.
It is not clear whether the increased uptake after local injection results from diffusion through an altered perineurium or access to the endoneurium at the site of nerve transection, proximal to the injection site. The latter explanation seems unlikely, because we did not observe fluorescein tracking up to the more proximal portions of the nerve. Olsson and Kristensson\(^{19}\) found that Evans blue albumin (MW 6,600) diffused across an area of crush injury to the rat sciatic nerve as long as 30 days after the injury, but there was minimal transfer of the material when applied distal to the injured site. On the other hand, Weerasuriya \textit{et al.}\(^{11}\) found that there was an eightfold increase in permeability to sodium and a fourfold to sixfold increase in permeability to glucose at a site distal to sciatic nerve transection in frogs. These changes were not seen 3 days after injury but were present 4–6 weeks after transection. It is possible that fluorescein, like sodium, can diffuse across the perineurium distal to a site of transection, whereas the larger albumin molecule can not. In addition, the elapsed time after nerve injury is an important variable. A study by Myers \textit{et al.}\(^{20}\) explored the effect of lead-induced nerve injury on sciatic nerve permeability. They found that fluorescein isocyanate-dextran of increasing molecular weight appeared intraneurally at different intervals after intravenous injection, with the MW 3,000 appearing at 7 weeks, MW 20,000 at 8 weeks, and MW 70,000 at 9 weeks.

Uptake into the cord remained very low in SNL animals after intravenous or epidural injection, even at cord levels containing afferent fiber terminals from the injured segments.

Intrathecal fluorescein results in high uptake into the intrathecal portion of the nerve root and the proximal portion of the DRG, with significantly lower penetration distally. This indicates incomplete delivery of agents to the cell bodies of sensory neurons via the cerebrospinal fluid, at least during the 30-min time course of this study. Furthermore, nonspecific effects of agents delivered by this route can be expected, because high levels of fluorescein accumulate in the cord. Klatzo \textit{et al.}\(^{21}\) also demonstrated uptake of intrathecally administered fluorescein isothiocyanate–labeled albumin and gamma globulin into the spinal nerve roots and DRGs but did not comment on the distribution of fluorescent material from proximal to distal.

One potential weakness of this study is that we looked at only one time interval between injection and fixation. We selected the 30-min time course as well as the fluorescein concentrations used based on previous studies as well as on our own pilot studies. It is possible that optimal accumulation may have occurred at either shorter or longer intervals and that different intervals might have revealed different distribution patterns in the tissues studied.

There is an obvious concern regarding the validity of the fluorescein model in predicting access of potentially useful drugs to DRGs or injured peripheral nerves. Although we can not extrapolate our findings to specific therapeutic agents, we believe that it is likely that a wide range of drugs, including ones that do not cross blood–brain or blood–nerve barriers, do gain access to the DRG or to injured peripheral nerves after regional or intravenous injection, including large molecules such as dextrans and proteins. Drugs that affect sodium, calcium, or potassium conductance or that block or reverse the effect of proinflammatory cytokines could have considerable therapeutic benefit when administered soon after a nerve injury. If these drugs produce unacceptable side effects when given systemically, they might provide a better therapeutic index when administered regionally. Techniques for injection of corticosteroids at lumbar and cervical spinal nerve foramina are now well established in humans\(^{22,25}\) and these methods can be easily modified to allow for intermittent or continuous application of other therapeutic agents. Patients with implanted intrathecal drug infusion systems might benefit from the addition of agents that target the DRG as well as the spinal cord. Patients receiving postoperative epidural infusions of local anesthetics and opioids could have drugs added that block the development of chronic pain. These approaches could be particularly useful for surgical procedures associated with a high likelihood of neuropathic pain, such as limb amputation and lateral throracotomy.

\section*{References}


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