

# Early Onset of Spontaneous Activity in Uninjured C-Fiber Nociceptors after Injury to Neighboring Nerve Fibers

Gang Wu,<sup>1</sup> Matthias Ringkamp,<sup>1</sup> Timothy V. Hartke,<sup>1</sup> Beth B. Murinson,<sup>2</sup> James N. Campbell,<sup>1,4</sup> John W. Griffin,<sup>2,3</sup> Richard A. Meyer<sup>1,4</sup>

Departments of <sup>1</sup>Neurosurgery, <sup>2</sup>Neurology, <sup>3</sup>Neuroscience, and <sup>4</sup>the Applied Physics Laboratory, Johns Hopkins University, Baltimore, Maryland 21287

Ligation and transection of the L5 spinal nerve in the rat lead to behavioral signs of pain and hyperalgesia. Discharge of injured nociceptors has been presumed to play a role in generating the pain. However, A fibers, but not C fibers, in the injured L5 spinal nerve have been shown to develop spontaneous activity. Moreover, an L5 dorsal root rhizotomy does not reverse this pain behavior, suggesting that signals from other uninjured spinal nerves are involved. We asked if abnormal activity develops in an adjacent, uninjured root. Single nerve fiber recordings were made from the L4 spinal nerve after ligation and transection of the L5 spinal nerve. Within 1 d of the lesion, spontaneous activity developed in approximately half of the C fiber afferents. This spontaneous activity was at a low level (median rate, seven action potentials/5 min), originated distal to the dorsal root

ganglion, and was present in nociceptive fibers with cutaneous receptive fields. The incidence and level of spontaneous activity were similar 1 week after injury. The early onset of spontaneous activity in uninjured nociceptive afferents could be the signal that produces the central sensitization responsible for the development of mechanical hyperalgesia. Because L4 afferents come along with degenerating L5 axons in the peripheral nerve, we hypothesize that products associated with Wallerian degeneration lead to an alteration in the properties of the adjacent, uninjured afferents.

**Key words:** neuropathic pain; nerve injury; sensitization; hyperalgesia; neuropathy; Wallerian degeneration; unmyelinated cutaneous afferent; in vivo; single nerve fiber recording

Pain is a devastating consequence of certain nerve injuries. Animal models have allowed the physiological basis of this pain to be investigated. One such model, transection of the L5 spinal nerve in rat, produces behavioral signs of neuropathic pain, including hyperalgesia to mechanical and thermal stimuli. This hyperalgesia is thought to be caused by an enhanced responsiveness of neurons in the nociceptive pathway at the level of the spinal cord and possibly higher. The peripheral signal that initiates and maintains this central sensitization is currently under debate.

Many authors argue that central sensitization is initiated by a barrage of neural activity in C-fiber afferents (Woolf, 1992). However, L5 dorsal root recordings after a lesion to the L5 spinal nerve revealed spontaneous activity only in A-fiber afferents; no spontaneous activity was found in injured C-fiber afferents (Boucher et al., 2000; Liu et al., 2000). In a previous study of monkeys, we found that an L6 spinal nerve lesion led to the development of spontaneous activity and adrenergic sensitivity in uninjured, cutaneous C-fiber nociceptors, which arose from adjacent intact roots (Ali et al., 1999). Because uninjured and degenerating fibers come along in peripheral nerves after a spinal nerve lesion, we hypothesize that the presence of neighboring degenerating nerve fibers leads to a change in the properties of the intact afferents. In this study, we investigated whether unin-

jured afferents from the L4 spinal nerve in the rat develop spontaneous activity after an adjacent L5 spinal nerve lesion.

## MATERIALS AND METHODS

**Experimental animals.** Sixteen male Sprague Dawley rats weighing 200–300 gm were studied. Two to four animals were placed in plastic cages with sawdust bedding and housed in a climate-controlled room under a 14/10 hr light/dark cycle. The Johns Hopkins University Animal Care and Use Committee approved the experimental protocol.

**Surgical procedures for producing the neuropathic pain model.** Deep anesthesia was induced with pentobarbital (50 mg/kg, i.p.) and maintained with supplemental doses. The left spinal nerve L5 was ligated and cut as described previously (Li et al., 2000). An incision was made above the lumbar spine, and the left transverse process of L6 vertebra was exposed. Removal of the L6 process exposed the ventral ramus of spinal nerves L4 and L5. The L5 mixed spinal root, just distal to the take off of the dorsal primary ramus, was isolated, tightly ligated with 6–0 silk suture, and cut ~1 mm distal to the suture. We call this lesion a modified spinal nerve ligation (SNL) because a similar model, developed by Kim and Chung (1992), involved ligation of L5 and L6 spinal nerves. For the sham surgery, the L5 ventral ramus was exposed but not ligated.

**Electrophysiological procedures.** The rats were initially anesthetized

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Correspondence should be addressed to Richard Meyer, 5-109 Meyer Building, Department of Neurosurgery, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287. E-mail: rmeyer@jhmi.edu.

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with pentobarbital (50 mg/kg, i.p.). The jugular vein was cannulated for subsequent intravenous administration of pentobarbital ( $8\text{--}10\text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ) to maintain anesthesia. Heart rate was continuously monitored by an electrocardiogram and used as an indicator of adequate anesthesia. In some animals, the carotid artery was cannulated for monitoring of blood pressure. A tracheotomy was performed, and animals were artificially ventilated to maintain expired  $\text{pCO}_2$  to 40 mmHg. Muscle relaxation was induced by an intravenous dose of pancuronium bromide (1 mg/kg) and maintained by supplemental doses hourly. Animal core temperature was measured by a rectal probe and maintained at  $38^\circ\text{C}$  using feedback-controlled, water-perfused heating pads.

Electrophysiological recordings were made from the L4 spinal nerve. Teased-fiber recording techniques were used as described previously (Campbell and Meyer, 1983). Briefly, the L4 spinal nerve was exposed using care to minimize disruption of the scar tissue surrounding the L5 spinal nerve. The sciatic nerve was exposed, and a stimulating electrode was placed under the nerve,  $\sim 2\text{ cm}$  distal to the recording electrode. The skin around the incision was used to form a pool by suturing the edges to a metal ring. The pool was filled with warm paraffin oil. A splitting platform, which also served as the ground electrode, was placed underneath the nerve, and a small silver wire that served as the recording electrode was positioned above the splitting platform. Small bundles were cut from the nerve, and the distal stump was teased into small filaments suitable for recording activity from single fibers.

The neural signal was differentially amplified, filtered, and digitized at a rate of 25 kHz. A real-time computer-based data acquisition and processing system (DAPSYS; Brian Turnquist, Johns Hopkins University, Baltimore, MD) provided multiple window discriminators for real-time sorting of different action potential (AP) waveforms (for details, go to <http://www.dapsys.net>). In addition, all waveforms passing a selectable threshold level were saved for *post hoc* analysis. The recorded responses were time-indexed relative to stimulus delivery by the stimulus control software.

The stimulation electrode was used to deliver electrical pulses of variable strength to the nerve to count the C fibers on the recording electrode. These numbers were used to estimate the proportion of spontaneously active C fibers. For some filaments, a count was not obtained or there were too many C fibers on the filament to obtain an accurate count.

## RESULTS

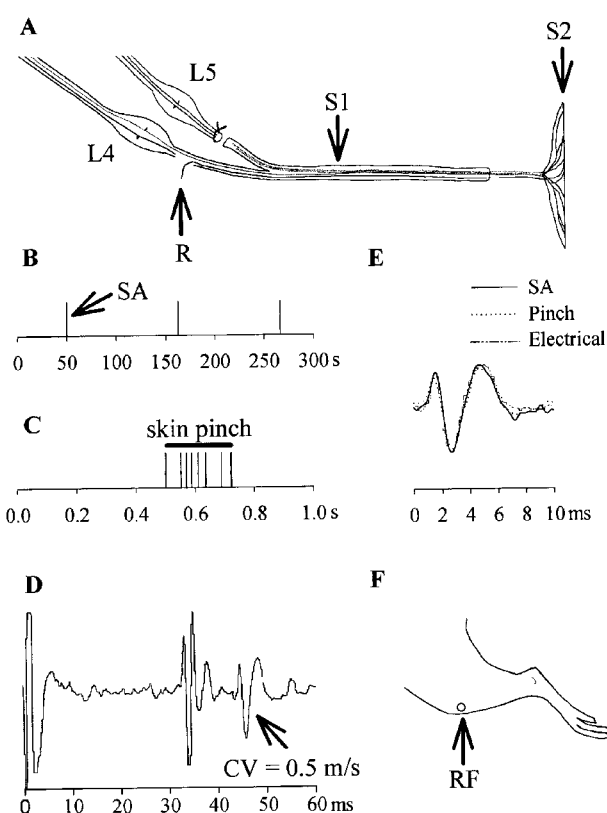
Single fiber recordings from the L4 spinal nerve were performed in untreated, control animals ( $n = 4$ ), in animals 1 d ( $n = 3$ ), 2 d ( $n = 3$ ), and 1 week ( $n = 4$ ) after ligating and cutting the L5 spinal nerve, and in animals 1 week ( $n = 2$ ) after a sham lesion to the L5 spinal nerve. The presence of spontaneous action potential activity in C fibers was assessed over a 5 min recording interval. In two fibers, spontaneous activity was stopped by gentle warming of the skin; they were therefore considered to be cold fibers (Leem et al., 1993) and excluded from this analysis.

### Spontaneous activity develops in uninjured C-fiber afferents

An example of a C fiber with low-grade (3 APs/5 min) spontaneous activity 2 d after an L5 spinal nerve lesion is shown in Figure 1. For this filament, only three C fibers were present on the recording electrode. One of these C fibers (conduction velocity 0.5 m/sec) had an action potential waveform that matched the action potential waveform of the spontaneously active fiber. The same waveform also was elicited by mechanical stimulation of a punctate cutaneous receptive field on the knee, providing evidence that the spontaneous activity originated from this cutaneous afferent.

### Spontaneous activity develops within 1 d of the lesion

We used two measures to estimate the incidence of spontaneous activity in C fibers: (1) the proportion of spontaneously active C fibers for those filaments in which we could determine the total number of C fibers, and (2) the incidence of filaments that had at least one spontaneously active C fiber. The second measure



**Figure 1.** Spontaneous activity in a typical C-fiber afferent recorded 2 d after an L5 spinal nerve lesion. *A*, Teased-fiber techniques were used to record activity from single nerve fibers of the L4 spinal nerve (*R*) in normal animals and in animals after ligation and transection of the L5 spinal nerve. *B*, The presence of spontaneous action potential activity (*SA*) was assessed over a 5 min recording interval. For this example, low-level spontaneous activity (3 action potentials/5 min) was present in one C-fiber afferent. *C*, The fiber with spontaneous activity also responded to pinching of the skin. *D*, Electrical stimulation at the sciatic nerve (*S1*) produced three discrete action potential waveforms at C-fiber latencies (2 are superimposed at 32 msec). *E*, The action potential waveform at 43 msec had the same shape as the spontaneous and mechanically induced activity providing evidence that the spontaneous activity came from this C-fiber nociceptor. *F*, The receptive field (*RF*) for this afferent was located near the knee. Thus, in this filament, one of three C fibers was spontaneously active.

included those filaments for which an accurate count of the number of C fibers was not obtained.

High-frequency spontaneous activity in A fibers, consisting mainly of muscle afferents, was frequently observed in the L4 recordings from both normal and lesioned animals (Table 1). The

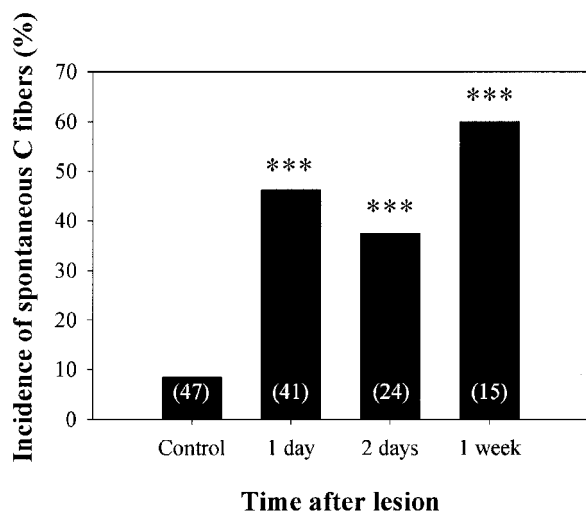
**Table 1. The incidence of filaments with spontaneous C-fiber activity in the L4 spinal nerve increased after an L5 nerve lesion**

Group	Number of rats	A fibers <sup>a</sup>	C fibers <sup>b</sup>
Untreated control	4	58% (46/79)	18% (4/22)
1 d after lesion	3	50% (33/66)	78% (14/18)***
2 d after lesion	3	52% (15/29)	90% (9/10)***
1 week after lesion	3	72% (36/50)	100% (18/18)***

<sup>a</sup>Spontaneous A-fiber activity came mostly from muscle afferents.

<sup>b</sup>C-fiber spontaneous activity could be assessed only in filaments without high-frequency spontaneous activity in A fibers.

\*\*\* $p \leq 0.001$  versus control ( $\chi^2$  test).



**Figure 2.** Increased incidence of spontaneously active C fibers occurs within 1 d of lesion. The proportion of spontaneously active C fibers recorded in the L4 spinal nerve is plotted as a function of time after the L5 spinal nerve lesion. Approximately half of the C fibers were spontaneously active within 1 d of the lesion ( $***p \leq 0.005$  vs control;  $\chi^2$  test). The total number of C fibers counted from electrical stimulation of the nerve is indicated in the parentheses. Only filaments in which the total number of C fibers could be counted were included. Each animal was represented by at least one filament.

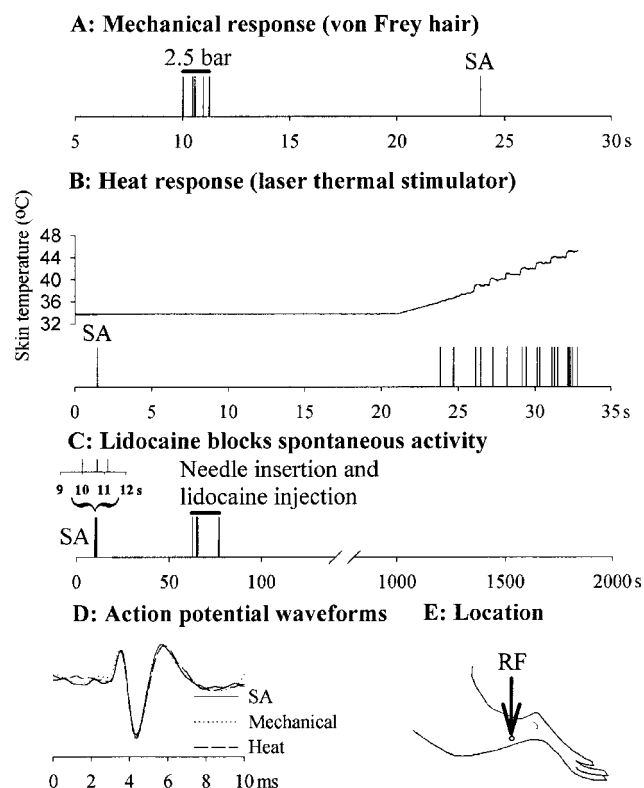
incidence of filaments containing spontaneously active A fibers was not significantly different in lesioned and control animals. Spontaneous activity in A fibers prohibited C-fiber conduction velocity surveys because of interference between spontaneous and electrically evoked waveforms. Therefore, the analysis of C-fiber spontaneous activity was restricted to those filaments in which A-fiber spontaneous activity was absent or present at a very low frequency. The incidence of filaments with spontaneous activity in C fibers increased significantly 1 d after lesion (Table 1) and remained elevated at 2 d and 1 week after lesion.

Less than 10% of the C fibers in the L4 spinal nerve were spontaneously active in uninjured, control animals (Figure 2). However, almost half of the C fibers became spontaneously active within 1 d of the L5 lesion. For all time points after the lesion (i.e., 1 d, 2 d, and 1 week), the proportion of spontaneously active C fibers was significantly higher than for control animals ( $p \leq 0.005$ ;  $\chi^2$  test). One week after sham surgery, the proportion of spontaneously active C fibers (3 of 53) was significantly lower than in lesioned animals at the same time point (9 of 15;  $p \leq 0.001$ ,  $\chi^2$  test).

The median discharge frequency in the spontaneously active C fibers, recorded 1 d after the lesion, was low (median, seven APs/5 min; range, 1–35 APs/5 min). The discharge frequency did not change substantially with time (median, 11 APs/5 min at 1 week). Approximately 40% of the C fibers exhibited a bursting discharge pattern (Fig. 3C). For these fibers, high-frequency bursts of 2–10 APs with instantaneous frequencies as high as 5 Hz were followed by long silent periods. The remaining fibers exhibited a low-grade, irregular discharge pattern (Fig. 1B).

### Spontaneous activity occurs in nociceptive afferents

In all but one experiment, we did not aggressively stimulate the skin to locate and characterize the receptive field of the spontaneously active C fibers. We took this conservative approach to avoid potential peripheral sensitization associated with repeated



**Figure 3.** Spontaneous activity originates at the receptive field of cutaneous, nociceptive afferents. *A*, Mechanical stimulation of this C-fiber nociceptor with a 2.5 bar von Frey probe results in a vigorous response. *B*, Heat stimulation (1°C/sec ramp from baseline temperature to 38°C, followed by 1°C step, 1 sec staircase to 45°C via a laser thermal stimulator) (Meyer et al., 1976) results in a graded response to heat. The first action potential occurred when the ramp temperature was 36°C. *C*, Intracutaneous injection of lidocaine (2% in 30  $\mu$ l) into the receptive field abolished the spontaneous activity for >30 min. Although the average rate of spontaneous activity in this fiber was low (9 APs/5 min), high-frequency bursts of activity were often observed. *Inset*, A burst of three spontaneous action potentials occurred 1 min before the lidocaine injection. *D*, The action potential waveforms from spontaneous activity, the mechanically evoked response, and the heat-evoked response matched. *E*, The punctate receptive field was located on the calf.

noxious stimulation that might influence the incidence of spontaneous activity. For one animal (not included in the incidence data), we changed this strategy and characterized the receptive field properties of all afferents with spontaneous activity 1 week after the L5 spinal nerve lesion. Skin pinching was used to locate the receptive field. Of eight spontaneously active C fibers, five had receptive fields responsive to intense mechanical and/or heat stimuli and therefore would be classified as nociceptors (Fig. 3). The receptive fields of the remaining three spontaneously active fibers could not be located; they may have been mechanically insensitive afferents (Handwerker et al., 1991; Meyer et al., 1991), or their receptive fields may not have been accessible for stimulation.

### Spontaneous activity originates distal to the dorsal root ganglion

Because teased-fiber recordings were made from the decentralized end of the spinal nerve, the spontaneous activity had to originate distal to the dorsal root ganglion. For some fibers (two of three tested), intracutaneous injection of lidocaine (2%, 30  $\mu$ l)



abolished the spontaneous activity (Fig. 3C), indicating that the spontaneous activity originated in the distal terminals.

## DISCUSSION

This is the first demonstration that spontaneous activity in uninjured C-fiber nociceptive afferents from the L4 spinal nerve develops within 1 d of a lesion to the L5 spinal nerve. Neuropathic pain behavior also develops within 1 d of an L5 lesion (Kim and Chung, 1992; Liu et al., 2000). Thus, this early onset spontaneous C-fiber activity could provide the signal that initiates the central sensitization responsible for the mechanical hyperalgesia. This C-fiber spontaneous activity could also be responsible for ongoing pain in these animals.

### Ectopic activity in injured axons

Peripheral nerve injuries lead to many changes in the properties of the injured axons. The regenerating nerve sprout exhibits ectopic mechanical, thermal, and chemical sensitivity as well as spontaneous activity (Blumberg and Jänig, 1984; Koschorke et al., 1991). In mixed nerves, the spontaneous activity is predominantly in myelinated afferents that originally innervated muscle and joints (Proske et al., 1995; Michaelis et al., 2000). However, low-grade spontaneous activity in C fibers has been reported after injuries to cutaneous nerves (Meyer et al., 1985). Surprisingly, ligation of the L5 spinal nerve appears to produce spontaneous activity only in A-fiber afferents; this has led to the speculation that A-fiber spontaneous activity could initiate central sensitization (Boucher et al., 2000; Liu et al., 2000). Possibly, more proximal lesions have a lesser liability for invoking spontaneous activity in C fibers. Alternatively, difficulties in recording from C fibers in the dorsal root could make these data less reliable.

Regardless, recent behavioral data suggest that signals that originate from the injured spinal nerve are not essential for hyperalgesia to occur. An L5 dorsal rhizotomy immediately before or after an L5 spinal nerve ligation did not prevent or reverse neuropathic behavior (Eschenfelder et al., 2000; Li et al., 2000). These behavioral results suggest that input from other sources including uninjured nerves may be involved in the signal that initiates and maintains the neuropathic pain behavior.

### Changes in uninjured primary afferent fibers

We demonstrate that spontaneous activity develops in uninjured, unmyelinated afferents in the rat L4 spinal nerve after a lesion to the L5 spinal nerve. Similar levels of spontaneous activity were reported in uninjured, unmyelinated fibers in a primate model of neuropathic pain (Ali et al., 1999).

In addition to the presence of spontaneous electrical activity, there is upregulation of a number of genes in the uninjured L4 dorsal root ganglion after an L5 spinal nerve lesion. There is an increased expression of mRNA for the vanilloid receptor 1 in L4 dorsal root ganglion neurons (Fukuoka et al., 2000b). This may account for the low heat threshold seen in some afferents (Fig. 3B). The mRNA for calcitonin gene-related peptide is upregulated in small- to medium-sized L4 dorsal root ganglion neurons (Fukuoka et al., 1998). Furthermore, PN3, a sodium channel subunit that is resistant to tetrodotoxin, is upregulated in large-diameter cells (Porreca et al., 1999; Boucher et al., 2000). Increased expression of mRNA for brain-derived neurotrophic factor (Fukuoka et al., 2000a) and for  $\alpha_{2A}$  adrenergic receptors (Xie et al., 2000) has also been reported.

### Activity in C fibers originates distal to the dorsal root ganglia

The ectopic spontaneous activity that develops in A fibers in both the injured L5 root and the uninjured L4 root appears to originate, at least in part, from the dorsal root ganglia (Boucher et al., 2000; Liu et al., 2000). In contrast, we demonstrate that the spontaneous activity in C fibers of the L4 root originates distal to the dorsal root ganglion. Boucher et al. (2000) reported that spontaneous C-fiber activity was not seen in L4 dorsal root recordings after an L5 lesion. However, in their experiments, the L4 spinal nerve was acutely cut at the time of the recordings, and therefore spontaneous activity originating from the periphery would not be recorded. Preliminary experiments from our laboratory (Wu et al., 2000) indicate that the incidence of spontaneous activity in dorsal root recordings is not greater than that from spinal nerve recordings, suggesting that spontaneous activity in nociceptive C fibers did not develop in the dorsal root ganglia.

Distal therapies such as topical capsaicin (Robbins et al., 1998) or lidocaine (Fields et al., 1998) are beneficial in certain patients with neuropathic pain. Our observations of spontaneous activity originating from cutaneous nociceptor terminals provide a rationale for these treatments. Similarly, these spontaneously active nociceptors may correspond to the irritable nociceptors that are thought to account for certain forms of postherpetic neuralgia (Fields et al., 1998).

### Spontaneous activity in C fibers produces central sensitization

Several authors have demonstrated that selective activation of nociceptors is needed to produce the central sensitization responsible for secondary hyperalgesia. For example, topical application of capsaicin or mustard oil selectively activates nociceptors and produces secondary hyperalgesia (Kilo et al., 1994; Koltzenburg et al., 1994). In addition, electrical stimulation of the peripheral nerve at C-fiber, but not A-fiber strength, produces central sensitization (Woolf, 1992).

In our study, the L5 lesion led to the development of low levels of spontaneous activity (median, seven APs/5 min) in a large proportion of the C-fiber population. Evidence that these low levels may be sufficient to initiate and maintain central sensitization comes from studies of secondary hyperalgesia produced by gentle heating stimuli; secondary hyperalgesia was produced by long-duration heat stimuli that were below threshold for producing heat pain (Cervero et al., 1993).

### Wallerian degeneration hypothesis

We postulate that Wallerian degeneration in the peripheral nerve plays an important role in neuropathic pain. In the SNL model, distal nerves of the sciatic distribution contain axons from both L4 and L5 roots in immediate juxtaposition. Acute injury to the L5 nerve root results in degeneration of myelinated and unmyelinated axons so that intact axons from the L4 root are exposed to a dramatically altered endoneurial environment. Morphological evidence suggests that Remak bundles in the hindpaw contain C fibers from more than one spinal root (Murinson et al., 2000). Transection of the L5 root produces a population of partially denervated Remak bundles that consist of degenerating axons from the L5 root and intact axons from the L4 root. The Schwann cells of these Remak bundles may respond to denervation via growth factors [e.g., nerve growth factor (NGF) and/or glia cell line-derived neurotrophic factor], cytokines (e.g., tumor necrosis factor- $\alpha$ ) and short-acting intermediators (e.g., ATP). For exam-

ple, increased NGF produced by Schwann cells and taken up by surviving C fibers could be transported back to L4 sensory nerve cell bodies where induced expression of receptor proteins could result in increased excitability. This would produce hyperalgesia as well as central sensitization. Alternatively, products from neighboring degenerating large fibers, their Schwann cells, or infiltrating macrophages may alter nociceptor function. Finally, denervation-induced changes in cutaneous cells (Li et al., 1997) might be involved. Whatever the mechanism, spontaneous activity in C-fiber nociceptors may be especially relevant to slowly progressive degenerative neuropathies involving small nerve fibers, many of which have spontaneous pain and hyperalgesia.

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