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Role of Different Peripheral Components in the Expression of Neuropathic Pain Syndrome

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Abstract

Peripheral nerve injury frequently leads to neuropathic pain like hyperalgesia, spontaneous pain, mechanical allodynia, thermal allodynia. It is uncertain where the neuropathic pain originates and how it is transmitted to the central nervous system. This study was performed in order to determine which peripheral component may lead to the symptoms of neuropathic pain. Under halothane anesthesia, male Sprague-Dawley rats were subjected to neuropathic surgery by tightly ligating and cutting the tibial and sural nerves and leaving the common peroneal nerve intact. Behavioral tests for mechanical allodynia, thermal allodynia, and spontaneous pain were performed for 2 weeks postoperatively. Subsequently, second operation was performed as follows: in experiment 1, the neuroma was removed; in experiment 2, the dorsal roots of the L4-L6 spinal segments were cut; in experiment 3, the dorsal roots of the L2-L6 spinal segments were cut. Behavioral tests were performed for 4 weeks after the second operation. Following the removal of the neuroma, neuropathic pain remained in experiment 1. After the cutting of the L4-L6 or L2-L6 dorsal roots, neuropathic pain was reduced in experiments 2 and 3. The most remarkable relief was seen after the cutting of the L2-L6 dorsal roots in experiment 3. According to the fact that the sciatic nerve is composed of the L4-L6 spinal nerves and the femoral nerve is composed of the L2-L4 spinal nerves, neuropathic pain is transmitted to the central nervous system via not only the injured nerves but also adjacent intact nerves. These results also suggest that the dorsal root ganglion is very important in the development of neuropathic pain syndrome.

Key Words: Neuropathic pain, animal model, allodynia, spontaneous pain, dorsal root ganglion, neuroma

INTRODUCTION

It has been shown that peripheral nerve injury or soft-tissue injury can cause severe chronic pain in humans.[1-3] This pain syndrome has a rapid onset of spontaneous, constant, and burning pain that may be easily exacerbated by light mechanical stimulation, temperature change and emotional disturbances.[2-4] However, it is uncertain where the neuropathic pain originates and how it is transmitted to the central nervous system.

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An injury of the peripheral nerve at a site distal to the dorsal root ganglion (DRG) morphologically produces a neuroma on the proximal stump of the injured nerve.[5-7] This neuroma is a tangled mass of regenerative axonal sprouts embedded within the connective tissue of a completely or partially transected peripheral nerve. The axons within a neuroma not only fail to reinnervate their original targets, but may also develop abnormal electrical hyperexcitability.[5,8] Thus, neuromas may serve as a generator of painful impulses. In contrast, there is evidence that DRG may take a part in the generation of neuropathic pain.[9-13] Therefore, both neuromas and DRG neurons with injured axons may be sources of neuropathic pain but the role of these peripheral components in neuropathic pain has remained to be determined.

Recently, we developed a neuropathic pain rat model employing distal sciatic nerve branch injury.[14] In our neuropathic pain model, the tibial and sural nerves were transected and the common peroneal nerve was left intact. The rats show vigorous ongoing spontaneous pain, mechanical allodynia, and cold allo-

dynia after injury. According to Green,[15] the sciatic nerve consists of the L4-L6 spinal nerves and the femoral nerve contributes to the L2-L4 spinal nerves. The L4-L6 spinal nerves contain injured fibers from the tibial and sural nerves and the L2-L4 spinal nerves receives somatic information from the femoral nerve which innervates sensitive areas located in the medial part of the paw. In this case, neuromas produced at the cut end of the tibial and sural nerves may be source of neuropathic pain. In contrast, the dorsal root ganglia of the L4-L6 or L2-L4 spinal segments may contribute to the generation of neuropathic pain. The present study was conducted in order to investigate the contribution of different peripheral components to neuropathic pain symptoms using our model of neuropathic pain.

MATERIALS AND METHODS

Subjects and neuropathic surgery

Eighty-one male Sprague-Dawley rats weighing 170−220 g were used. The animals were housed in groups of 4−5 in plastic cages with soft bedding under a 12-h light-dark cycle. The animals were kept at least 7 days before surgery. Under gaseous anesthesia with halothane, neuropathic injury was produced by tightly ligating and cutting the tibial and sural nerves, leaving the common peroneal nerve intact.[14] Hemostasis was confirmed and the wound was sutured.

Behavioral tests

Behavioral signs representing three different components of neuropathic pain (mechanical allodynia, cold allodynia and spontaneous pain) were examined in all the rats for 2 weeks postoperatively.

Mechanical allodynia: The rats were placed on a metal mesh floor under a transparent plastic dome (8 ×8×18 cm), and innocuous mechanical stimuli were applied to the sensitive area of the hind paw with a von Frey filament (8 mN of bending force). The most sensitive area was first determined by poking various areas of the paw with a von Frey hair. Next, the actual test was conducted by gently poking the spot with the filament. A von Frey filament was applied 10 times (once every 3−4 sec) to each hind paw. The frequency of foot withdrawal expressed in percentage was used as the index of mechanical allodynia.

Cold allodynia: To quantify the cold sensitivity of the paw, the rats were placed on a metal mesh floor under a transparent plastic dome and brisk paw withdrawal in response to acetone application was measured. The acetone was applied five times (once every 5 min) to each paw. The frequency of paw withdrawal expressed in percentage was used as the cold allodynia index.

Spontaneous pain: To measure spontaneous ongoing pain, each rat was placed on a acrylic plate under a transparent plastic dome at room temperature. After 5 min. of adaptation, the number of spontaneous withdrawal behaviors that the rat held its foot off the floor was used as the spontaneous ongoing pain index.

Second surgery

Following behavioral tests for neuropathic pain symptoms, the rats were subjected to second surgery for removing neuroma or cutting dorsal roots under gaseous anesthesia. The animals were divided into the following groups according to the type of surgery.

Experiment 1: effects of removing neuroma

Group A (removing neuroma, n=14); A suture was opened and the neuromas on the tibial and sural nerves were removed.

Group B (sham surgery for removing neuroma, n=14); A suture was opened but the neuromas were not removed.

Experiment 2: effects of cutting the dorsal roots of injured segments

Group C (L4-L6 dorsal rhizotomy, n=12); A laminectomy was performed at the L1-L6 levels. The dura matter was incised and the left L4-L6 dorsal roots (ipsilateral to the neuropathic surgery) were identified intradurally. The dorsal roots were sectioned by cutting with a pair of microscissors.

Group D (L4-L6 sham rhizotomy, n=7); The surgical procedure was the same as that of group C, with the exception of leaving the dorsal roots intact. All procedures, including a laminectomy, incision of the dura mater, and isolation of the dorsal roots, were done exactly as in group C.

Experiment 3: effects of cutting the dorsal roots of both intact and injured segments

Group E (L2-L6 dorsal rhizotomy, n=17); The sur-

gical procedure was the same as that of group C, but the left L2-L6 dorsal roots were cut instead of the L4-L6 dorsal roots.

Group F (L2-L6 sham rhizotomy, n=17); The surgical procedure was the same as that of group E, except for leaving the dorsal roots intact.

A complete hemostasis was confirmed and the wound was closed with muscle and skin sutures. Behavioral tests for neuropathic pain symptoms were conducted again 1, 4, 7, 14, 21, and 28 days after removal of neuroma or dorsal rhizotomy in order to compare the different groups.

RESULTS

Effects of removing neuroma (Experiment 1)

The results of behavioral tests for mechanical sensitivity of the paw in experimental groups A (Cut) and B (Sham) are shown in Fig. 1A. Before neuropathic injury, the rats were rarely responsive to the application of a von Frey filament (8 mN) which produces a sensation of light touch when applied to human skin. After injury of the tibial and sural nerves, the ipsilateral hind paw became sensitive to mechanical stimuli as evidenced by frequent lifts of the foot in response to the application of the von Frey filament. This increased sensitivity to innocuous mechanical stimuli was interpreted as a sign of mechanical allodynia. Fourteen days after injury of the tibial and sural nerves, removal of neuroma was accomplished. There was no difference between the A (removal of neuroma) and B (sham surgery) groups. The mechanical sensitivity to von Frey filaments was reduced slightly on the day following removal of neuroma, but recovered by the fourth day and remained high until the end of the test period. In actuality, the mechanical sensitivity tends to increase slightly.

Fig. 1B shows the results of behavioral tests for cold sensitivity of the paw. Following neuropathic injury of the tibial and sural nerves, the frequency of foot lifts to acetone application to the paw increased. This increased sensitivity to acetone application was interpreted as a sign of cold allodynia. After neuromas were removed, no significant difference between groups A (removal of neuroma) and B (sham surgery) was observed.

Fig. 1C shows the number of foot lifts on an acrylic plate at room temperature. The number of foot lifts on the plate increased after neuropathic injury of the tibial and sural nerves. After neuromas were removed, the signs of ongoing pain in the group of rats with the removal of neuroma were not reduced compared to the sham-operated control group and rather slightly increased after the second operation (Fig. 1C). In Fig. 1, the asterisks indicate values significantly different from the control (sham surgery) values at each time point. These results suggest that neuropathic injury of the tibial and sural nerves induces the development of behavioral signs indicating various

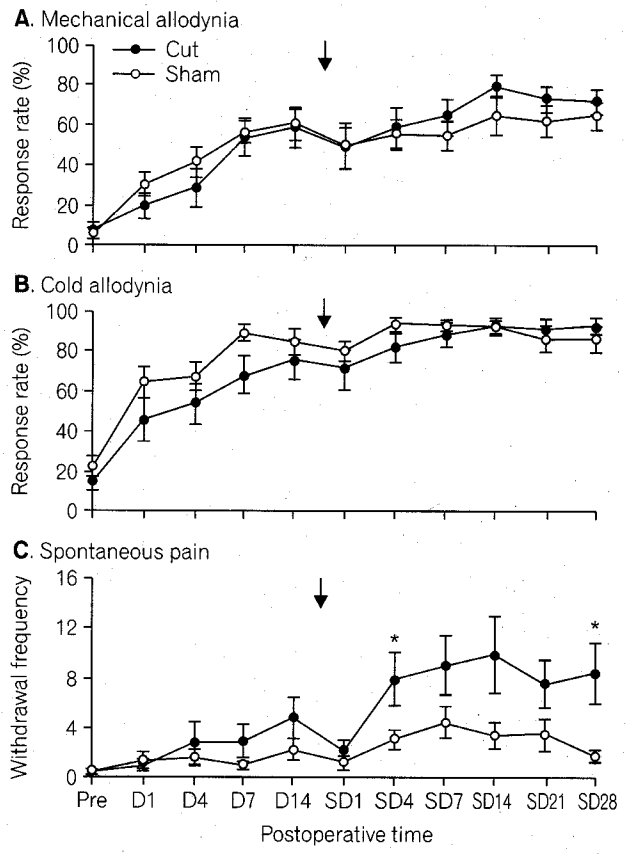

Fig. 1. Effects of removing neuroma on the expression of neuropathic pain. Response rate to von Frey filament and acetone was used as an index of mechanical allodynia (A) and cold allodynia (B), respectively. The spontaneous withdrawal frequency on the acrylic plate at room temperature was measured during a 5-minute observation period for spontaneous pain (C). Data are expressed as mean ±SE. Postoperative time is expressed as Pre for the preoperative control period or as D and SD for days after initial neuropathic surgery (the tibial and sural nerves injury) and second operation (removal of neuroma; indicated by an arrow), respectively. Groups A and B are shown as Cut and Sham, respectively. Asterisks indicate values significantly different from the sham control values ($p < .05$).

components of neuropathic pain and these signs are not significantly attenuated by the removal of neuroma.

Effects of L4-L6 dorsal rhizotomy (Experiment 2)

To determine the role of injured sensory neurons in the expression of neuropathic pain behaviors, their inputs to the spinal cord were blocked by cutting the dorsal roots of the injured segments (L4-L6). In contrast to the sham dorsal rhizotomy (Group D), transection of the L4-L6 dorsal roots (Group C), performed on the 14th PO day, significantly reduced mechanical allodynia (Fig. 2A). In Fig. 2, the asterisks indicate values significantly different from the control (sham surgery) values at each time point. Transection of the L4-L6 dorsal roots, however, was not effective in reducing cold allodynia (Fig. 2B) or spontaneous ongoing pain (Fig. 2C). The results indicate that spinal inputs from the injured segments may not be sufficient for the expression of neuropathic pain.

Effects of L2-L6 dorsal rhizotomy (Experiment 3)

In order to determine the relative contribution of intact sensory neurons to neuropathic pain behaviors, their inputs to the spinal cord were blocked by transecting the dorsal roots of the appropriate uninjured segments as well as the injured segments. Compared to the sham rhizotomy (Group F), transection of the L2-L6 dorsal roots (Group E) eliminated all tested neuropathic behaviors such as mechanical allodynia (Fig. 3A), cold allodynia (Fig. 3B), and spontaneous pain (Fig. 3C). In Fig. 3, the asterisks indicate values significantly different from the control (sham surgery) values at each time point.

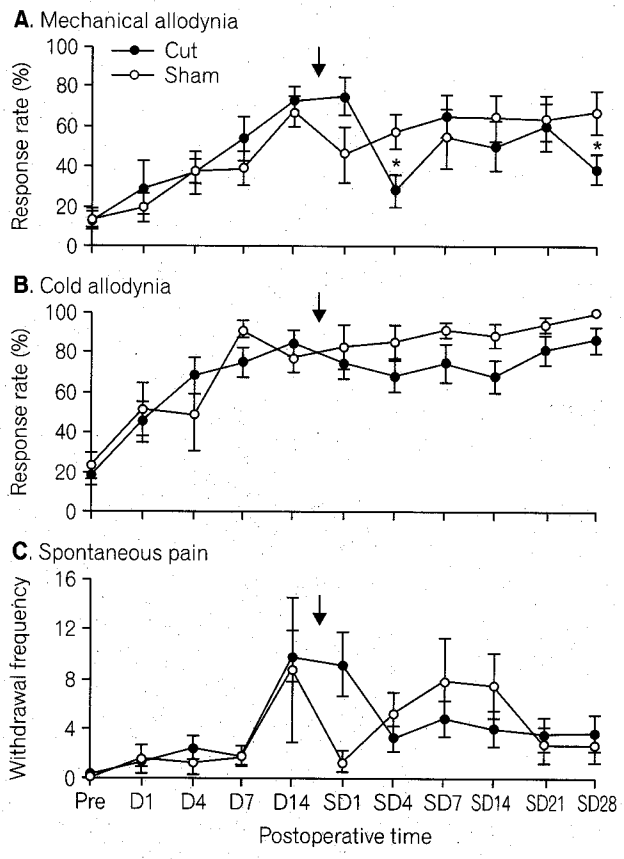

Fig. 2. Effects of transecting the L4-L6 dorsal roots on the expression of mechanical allodynia (A), cold allodynia (B), and spontaneous pain (C) are expressed as in Fig. 1. Groups C and D are shown as Cut and Sham, respectively. Asterisks indicate values significantly different from the sham control values ($p < .05$).

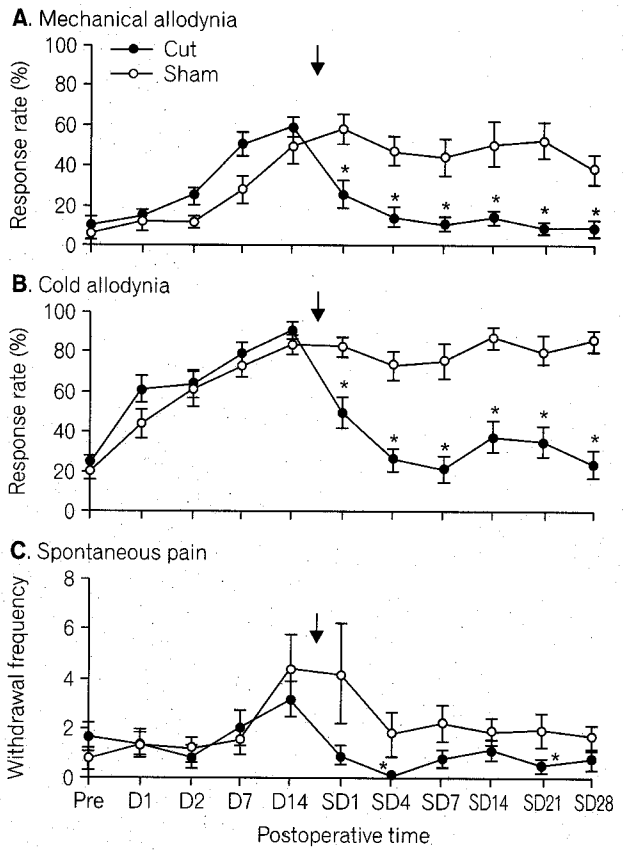

Fig. 3. Effects of transecting the L2-L6 dorsal roots on the expression of mechanical allodynia (A), cold allodynia (B), and spontaneous pain (C) are expressed as in Fig. 1. Groups E and F are shown as Cut and Sham, respectively. Asterisks indicate values significantly different from the sham control values ($p < .05$).

These results suggest that the behavioral signs of mechanical allodynia, cold allodynia, and spontaneous pain are dependent on signals entering the spinal cord from the intact as well as injured fibers of the peripheral nerves.

DISCUSSION

This study was intended to elucidate the role of different peripheral components on neuropathic pain using an animal model of neuropathic pain which we developed.[14] In our model of neuropathic pain, the tibial and sural nerves were cut and a neuroma was produced at the cut-end of each nerve. In order to determine the role of neuroma, DRG, and injured or intact neighboring afferent neurons in neuropathic pain behaviors, the transmission of their inputs to the spinal cord was blocked by either removal of the neuroma or transection of the dorsal roots of the injured and intact segments in the present study.

After the removal of neuroma, neuropathic pain was not relieved. On the contrary, after removal of neuroma, unexpectedly, neuropathic pain tends to increase (see Fig. 1A to 1C). This phenomenon appears to occur because the second surgery (removal of neuroma) may produce additional injury on the peripheral nerve.

According to DeLeo et al., freezing a peripheral nerve produces autotomy without scarring or neuroma formation.[16] This supports a view that the presence of a neuroma is not a prerequisite for the development of this behavior. This means that even sprouting from abnormal regeneration without neuroma formation may induce ectopic discharges potentiating DRG or spinal hyperactivity. Therefore, these results suggest that neuroma is not important in the generation of neuropathic pain.

While neuropathic pain was not significantly reduced by the removal of neuroma at the cut end of the tibial and sural nerves, it was reduced after the cutting of the L4-L6 or L2-L6 dorsal roots. The most remarkable relief was seen after the cutting of the L2-L6 dorsal roots. As DRGs are located between the dorsal roots and the peripheral nerves at the cut end of which a neuroma may be located, these results suggest that DRG is very important in the development of neuropathic pain syndrome.

Even though the mechanical allodynia and cold allodynia returned to preoperative baseline levels after the transection of the L2-L6 dorsal roots, the behavioral signs of allodynia were not completely eliminated. The reason why these responses to external stimuli could not be abolished is uncertain. However, three postulations may at least in part explain this phenomenon. First, the dorsal roots adjacent to the transected L2-L6 spinal levels may transmit the sensory information from the receptive field. Second, spontaneous foot lifting (due to either spontaneous pain or not) immediately after stimulation may be confounded with allodynia. Third, mammalian ventral roots have been demonstrated to contain a large number of afferent fibers.[17,18] Some of these ventral root afferent fibers enter the spinal cord directly through the ventral root.[19,20] Although it has been observed in neonatal rats, there is some evidence that the ventral root afferent fibers can sprout after sciatic injury.[21,22] These innate or sprouted afferent fibers in the ventral root may transmit the information from the receptive field.

It appears that the intact nerve involved in the production of neuropathic pain may be the femoral nerve rather than the common peroneal nerve. In our pilot study, the transection of the common peroneal nerve did not change any components of neuropathic pain. According to the fact that the sciatic nerve is composed of the L4-L6 spinal nerves and the femoral nerve contributes to the L2-L4 spinal nerves,[15] the L4-L6 dorsal roots transmit inputs from the injured fibers, the tibial and sural nerves each of which is one of the sciatic nerve branches, and the L2-L4 dorsal roots transmit inputs from intact fibers from the femoral nerve. Therefore, neuropathic pain is transmitted to the central nervous system via not only the injured nerve but also adjacent intact nerves.

In a similar study employing a spinal nerve ligation model in which the L5 and L6 spinal nerves were injured, Yoon et al.[23] reported that neuropathic pain behaviors including mechanical allodynia, cold allodynia and spontaneous pain, were eliminated by cutting the dorsal roots of the injured spinal nerves (L5 and L6) and that cutting the central root of the uninjured ganglion (L4) eliminated evoked responses, while having no influence on spontaneous pain. Our results are not consistent with their results in which the role of the injured and uninjured afferents was clearly separated. Other recent observations support our findings, although these studies used spinal nerve ligation mo-

dels. For example, Ali et al. observed that a subpopulation of uninjured unmyelinated afferents also developed ongoing actopic activity following spinal nerve ligation.[24] This observation suggested that in the presence of nerve injury, changes in uninjured afferents would be sufficient to initiate and maintain neuropathic pain behaviors. More directly, Li et al.[25] were unable to replicate the observation by Yoon et al.[23]. Therefore, as Gold[26] suggested, it is likely that the pain behaviors observed in the presence of nerve injury reflect activity in both the injured afferents and their uninjured neighbors.

In our model of neuropathic pain, however, the role of injured and uninjured afferents can be explained differently. It is well known that ectopic discharges are produced by injured nerve fibers and their DRG cells.[9,27] These ectopic discharges would then enter the spinal cord and sensitize the spinal dorsal horn neurons, since a sustained input caused by nerve and tissue injury is known to sensitize dorsal horn neurons.[28-32] The alteration of the central processing of sensory information by sensitization of the spinal cord seems to be essential for many sensory abnormalities including neuropathic pain.[33-35] In our model of neuropathic pain, the injured fibers of L4-L6 segments may contribute to this central sensitization process.

Of interest is the contribution of intact fibers to neuropathic pain. Peripheral nerve axons are capable of reinnervation to denervated areas after injury. It has been reported that there are two types of regenerative growth. One involves collateral innervation by neighboring intact fibers. For example, when the sciatic nerve is injured in rats, the saphenous nerve axons can sprout to expand their receptive field to the denervated areas.[36,37] Similarly, the teeth, mucous membrane and skin supplied by the inferior alveolar nerve in the adult cat are reinnervated by collateral sprouting after nerve section.[38] Partial denervation of the medial gastrocnemius muscle results in collateral sprouting by motor axons innervating endplates adjacent to the site of denervation. This axonal sprouting is associated with the upregulation of a developmentally regulated membrane-bound phosphoprotein, growth-associated protein-43 (GAP-43), in the denervated area.[39] The cutaneous collateral spread has also been described in human.[40] The other involves regenerative outgrowth of fibers severed by the injury. After the sciatic nerve is injured, the regenerating sciatic nerve can make a functional contribution. This can be seen by the return of sensation to zones not invaded by the saphenous nerve.[36] With the return of the sciatic nerve, the expanded distribution of the saphenous nerve goes back to its original boundaries. Of these two types of reinnervation, collateral sprouting seems to be involved in neuropathic pain symptoms, including allodynia and spontaneous pain. At a minimum, mechanical and thermal allodynia likely involve collateral sprouting because allodynia requires external inputs through sensory receptors and afferent axons. In any case, collateral sprouting could be useful by providing protective pain sensation to a denervated cutaneous area in situations where the injured axons can not reinnervate the denervated areas. In our model, the intact fibers of the L2-L6 segments (mainly the femoral nerve from the L2-L4 segments) may play a role in this process. Alternatively, physiological or morphological changes in the intact DRGs may play a role in producing neuropathic pain. Lee et al. demonstraded that there is an increase in the density of tyrosine hydroxylase-immunoreactive (TH-IR) fibers as well as the number of TH-IR-wrapped neurons in the completely intact, uninjured segment in the segmental spinal nerve ligation injury model.[13] These pathophysiological changes may be related to the production or maintenance of neuropathic pain.

Afferent signals from both intact and injured fibers can be integrated in the spinal cord and/or supraspinal sites. As evidence of involvement of supraspinal components, Sung et al.[41] have observed that spinal transection or hemisection of the spinal cord ipsilateral to the injured nerve drastically (but not completely) blocks the behavioral sign of mechanical allodynia. Porreca et al.[42] have shown that spinal cord transection blocks tactile allodynia in a loose nerve ligation model of neuropathic pain, and Kauppila[43] has provided evidence that spinalization reduces the mechanical hyperalgesia produced by sciatic nerve section. These results suggest that the generation of (at least mechanical) allodynia or hyperalgesia following partial peripheral nerve injury involves transmission and integration of the triggering sensory signals to a site rostral to the sectioned area. The mechanism of this integration remains to be determined.

In conclusion, our results suggest that DRG, rather than neuroma, is very important in the expression of neuropathic pain. The removal of sensory inputs from the injured segments alone was not sufficient to inhibit neuropathic pain. Instead, sensory inputs from

both the injured and intact segments appear to contribute to the expression of neuropathic pain. Pathophysiologically the injured and intact fibers may be involved in the central sensitization and the collateral sprouting process, respectively, and signals from both injured and intact fibers may interact in the central nervous system to produce neuropathic pain.

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