



## THE ROLE OF THE DORSAL COLUMNS IN NEUROPATHIC BEHAVIOR: EVIDENCE FOR PLASTICITY AND NON-SPECIFICITY

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**Abstract**—Despite conflicting clinical and experimental evidence, textbook description of somatic sensations continues to follow a rigid dichotomy based on the concept that pain sensation is transmitted cephalad primarily through anterolateral pathways, while touch is mediated through the dorsal column pathway. This study provides an example of the dynamic rerouting in the transmission of the nociceptive signals following injuries to the peripheral and central processes of sensory neurons. In two rat models for mononeuropathy, the chronic constriction injury model [Bennett, G.J., Xie, Y.K., *Pain* 33 (1988) 87–107] and the spared nerve injury model [Decosterd, I., Woolf, C.J., *Pain* 87 (2000) 149–158], we demonstrate that selective dorsal columns lesion produced significant decrease of tactile and cold allodynia and thermal hyperalgesia which were assessed by the Von Frey hair filaments, the acetone drop test and the heat-induced paw withdrawal, respectively. These manifestations, however, can reappear 2 weeks after bilateral dorsal column lesion in rats subjected to spared nerve injury mononeuropathy and appear also in animals sustaining chronic bilateral dorsal column lesion followed by either model of mononeuropathy. Lesion of the dorsal column on the side opposite to the neuropathic leg did not alter the neuropathic manifestations in both animal models. Changes in the sequence of timing of the dorsal column lesion and induction of mononeuropathy, suggest that the effects of the former last for 1 to 2 weeks.

The results of this study show that the dorsal columns are involved in neuropathic manifestations and at the same time are not necessary for their full development and persistence. Furthermore, these results shade doubts on the validity of the concept of segregation of pathways involved in the transmission of neuropathic manifestations. Therefore, principles governing acute pain transmission are not necessarily applicable to chronic pain situations. The latter conditions seem to engage other available pathways to reestablish the pain signaling system.

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For more than a century, it has been reported that transmission of somatic sensory information in the mammalian spinal cord is functionally segregated (Brown-Séquard, 1868; Bonica, 1990). Human cordotomy studies (Spiller and Martin, 1912; Gybels and Tasker, 1999), animal spinal cord lesion studies (Kennard, 1954; Mehler et al., 1960) and single unit electrophysiological experiments (Willis, 1986) all point to the duality of innocuous vs. noxious information transmission, with the dorsal columns (DCs) being the main route for transmission of tactile perception while the anterolateral path-

ways being more important in nociceptive information transmission. This functional segregation is not absolute, because nociceptive cells are found in the DC nuclei (Ferington et al., 1988; Willis et al., 1999), and in humans, where only the anterolateral white matter is preserved, there is a preservation of crude touch sensation (Wall and Noordenbos, 1978). Several lines of evidence support the concept that this segregation may not be preserved, at least totally, in neuropathic pain conditions, since the DC has been shown to be involved in rostral transmission of tactile allodynia while nociceptive information channeled through the C fiber system continues to be transmitted in the anterolateral system (Bian et al., 1998; Ossipov et al., 1999). The present study investigates the role of the DC in the transmission of tactile allodynia and its possible contribution to the segregation of somatic informations during neuropathic conditions.

Peripheral neuropathic pain is characterized by a constellation of syndromes including allodynia (pain produced by innocuous stimuli), hyperalgesia (increased sensitivity and responsiveness to noxious stimuli) that have been reproduced in several animal models (Bennett,

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Abbreviations: CCI, chronic constriction injury; DC, dorsal column; HP, hot plate; PW, paw withdrawal; PWD, paw withdrawal duration; PWL, paw withdrawal latency; SNI, spared nerve injury; SNL, spinal nerve ligation; VFF, Von Frey hair filaments.

1994; Kim et al., 1997; Ralston, 1998) and attributed to plastic changes affecting either the afferent fibers or their relay stations in the CNS (Gracely et al., 1992;Coderre et al., 1993; Scadding, 1999). These changes include peripheral and/or central sensitization (McMahon and Wall, 1984; Gracely et al., 1992; Cervero and Laird, 1996), sprouting of the peripheral (McMahon and Kett-White, 1991) or central (Woolf et al., 1995) processes of the injured or intact fibers and alteration in the function of the nervous centers involved in the processing of nociceptive information (Guilbaud et al., 1990; Urban and Gebhart, 1999; Ossipov et al., 2000).

As illustration of these plastic changes, two recent groups of evidence provide examples of drastic rerouting of nociceptive information under neuropathic conditions: firstly, the transmission of tactile allodynia by the DC-medial lemniscus system in mononeuropathic rats and its abolition by selective DC lesion or by block of DC neuronal activities (Bian et al., 1998; Miki et al., 1998, 2000; Sung et al., 1998; Ossipov et al., 2000); secondly, the activation of lamina I spinal nociceptive neurons and their relay stations in the parabrachial area by low-threshold mechanical or thermal inputs (Bester et al., 2000; Blomqvist and Craig, 2000).

The interpretation of the role of the DC in tactile allodynia is complicated by the fact that this may simply be an increase in responsiveness to touch which may or may not translate into pain perception. Here we examine the role of the DC system in mechanical, cold and heat neuropathic pain-related behaviors and show its involvement in all measures of pain which may involve cortical or brainstem circuitry. Using two rat models for mononeuropathy, we demonstrate that selective DC lesion can produce transient alteration in the resulting mechanical and thermal allodynia and hyperalgesia and provide evidence for the recurrence or appearance of these neuropathic manifestations after chronic DC lesion. This finding implies that the principles of organization of acute nociceptive transmission are not necessarily applicable in chronic pain conditions, and questions the validity of the concept of segregation of pathways involved in the transmission of neuropathic manifestations.

## EXPERIMENTAL PROCEDURES

All experiments were performed on adult Sprague-Dawley rats (average weight 250–300 g), housed in individual cages under optimal conditions with free access to food and water. Surgical interventions were performed under deep anesthesia with ketamine (Ketalar, 40–50 mg/kg, i.p.) which was preceded by pre-anesthesia with chlorpromazine (8 mg/kg, i.p.) and atropine (0.05 mg/kg, i.p.). All procedures complied with the ethical guidelines for pain experimentation on awake animals (Zimmermann, 1983) and were approved by the Institutional Animal Care Committee.

### Induction of mononeuropathy

Mononeuropathy was induced in different groups of rats following either the chronic constriction injury (CCI) model (Bennett and Xie, 1988) or the spared nerve injury (SNI) model (Decosterd and Woolf, 2000). The sciatic nerve was

exposed after sectioning the skin of the posterior aspect of the thigh and incision through the fat pad covering the popliteal fossa. For the CCI model, four loose ligations (4.0 chromic catgut), spaced by about 1 mm, were placed proximal to the sciatic trifurcation. For the SNI model, the common peroneal and the posterior tibial nerves were isolated, tightly ligated and sectioned, while the sural nerve supplying the lateral aspect of the leg was kept intact.

### Experimental groups and DC lesion

This study was based on observations obtained from 10 different rat groups ( $n=5-7$  each) subjected to either CCI (seven groups) or SNI (three groups).

Rats subjected to SNI mononeuropathy were distributed as one group for each of the following procedures: intact spinal cord ( $n=7$ ), bilateral DC lesion ( $n=7$ ) and unilateral DC lesion on the side opposite to the neuropathic leg ( $n=5$ ).

In a first set of experiments on rats subjected to CCI mononeuropathy, three groups were used as follows: one with intact spinal cord ( $n=7$ ), a second with unilateral DC lesion on the side opposite of neuropathic leg ( $n=5$ ) and a third ( $n=7$ ) with bilateral DC lesion 2 weeks after the induction of CCI in the left leg, and after 6 weeks the same rats were subjected to CCI in the second (right) leg.

The second set of experiments was devoted to the study of the effects of the timing of DC lesion on the incidence of neuropathic manifestation in the CCI model. One group of rats was used in each of the following four combinations: DC lesion 3 days following CCI ( $n=7$ ); DC lesion simultaneous with CCI ( $n=5$ ); or DC lesion preceding CCI by 1 ( $n=5$ ) or 2 ( $n=5$ ) weeks.

Selective DC lesions were performed on anesthetized rats at the C2–C3 level with the help of an operating microscope. After exposing the space between the first and the second cervical vertebrae and sectioning the dura matter, the separated tips (0.5–0.7 mm) of a jeweler's forceps were introduced on each side of the midline for a total depth of 0.5–0.7 mm and compressed twice. This operation resulted in an overt interruption of the fibers traveling in the medial dorsal aspect of the spinal cord and to a temporary block of blood circulation in the dorsal artery. For unilateral DC lesion, the same procedure was followed on one side of the spinal cord. After suturing the wounds by layers, the rats were allowed a recovery period of 1 week before resuming the behavioral tests. At the end of the observation period, the rats were perfused under deep anesthesia and their cervical spinal cords were isolated and processed for histological control. This study was based on observations made on rats with successful lesions involving all the gracile and most of the cuneate tracts and sparing the corticospinal tract descending deep in the DCs (Fig. 1). In few cases, however, the lesion involved parts of the corticospinal tract (Fig. 1C2) but this did not result in significant changes in the nociceptive behavior of these rats.

### Behavioral tests

Rats were placed in individual compartments of a cage with a floor made of a wire mesh allowing free access to stimulation with hair filaments to the foot pad and the lateral aspect of the leg.

For the mechanical allodynia, the plantar surface of the hind paws (lateral for the SNI model and mid-plantar for the CCI model) was probed with two Von Frey hair filaments (VFF) numbered 4.31 and 5.07 (Stoelting, IL, USA) corresponding to 2.041- and 11.749-g forces (18.5 and 106.7 mN, respectively). Bending forces of these filaments were shown to be insufficient to produce nociceptive withdrawal reflexes in normal animals (Decosterd and Woolf, 2000). The number of paw withdrawals (PWs) elicited per 10 trials was established for each rat on each hind paw before (baseline) and after the induction of the mononeuropathy. In normal rats, the low- (VFF 4.31) and the high- (VFF 5.07) caliber filaments produced an average of  $1.3 \pm 0.2$

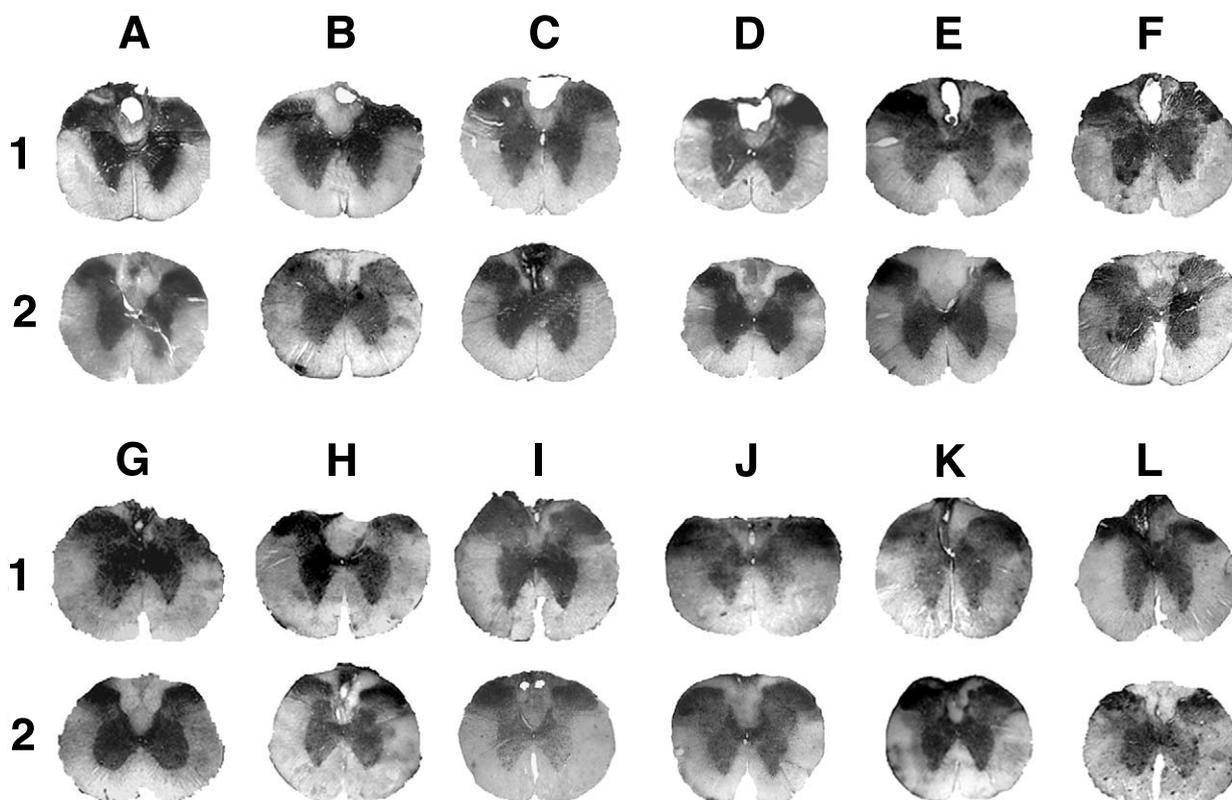


Fig. 1. Photomicrograph of selected spinal cord sections at upper cervical and caudal medullary levels illustrating the DCs lesions. Sections A–J show bilateral DC lesion while K and L illustrate unilateral DC lesion performed on the side contralateral to the neuropathic leg. Sections in row 1 were selected from a level rostral to the site of lesion to show the degenerating ascending fibers, while sections in row 2 were selected from a level caudal to the site of the lesion to show the intact corticospinal fibers descending deep in the DC, with the exception of rat C where the lesions affected partially the corticospinal fibers. All the sections were selected from rats subjected to CCI mononeuropathy.

and  $2.7 \pm 0.3$  paw responses per 10 trials, respectively. After the induction of neuropathy, both filaments elicited more than five responses per 10 trials.

For the cold allodynia, we followed the method described by Choi et al. (1994) which consisted of applying few drops ( $\approx 50 \mu\text{l}$ ) of acetone solution on the paw and measuring the duration of the withdrawal reaction. Half a second and 20 s were assigned as minimal and maximal cut-off points, respectively.

The latency (L) and the duration (D) of the PW in response to a nociceptive beam of radiant heat directed to the plantar surface were established in normal rats. The increase of PWD and/or the decrease in the PWL, after the induction of the mononeuropathy, were considered as an indication of the thermal hyperalgesia. Each rat was subjected to two PW tests per session separated by a minimum interval of 5 min.

The hot plate (HP) test was also used for the assessment of the thermal hyperalgesia. It consisted of placing each rat on a heated metal pad at  $53 \pm 0.3^\circ\text{C}$  and measuring the latency of its reaction as paw licking or jumping.

#### Data analysis

The allodynia and hyperalgesia were assessed for each rat in reference to measurements established before the induction of the neuropathy. As illustration for the mechanical allodynia, the number of PWs in 10 trials was averaged for each group of rats before the induction of the neuropathy and was compared to the average measured after the neuropathy; further comparisons were made between measurements on the lesioned and the intact legs. The significance of differences (baseline versus operated and operated versus intact legs) was calculated for each experimental group using ANOVA and Bonferroni post-hoc test.

## RESULTS

### General observations

Rats subjected to mononeuropathy following either the method of CCI of the sciatic nerve or the method of SNI displayed evident signs of neuropathy in the operated legs. These signs include abnormal position of the leg and limping, trophic changes (specially excessive growth of the nails) and evident allodynia and hyperalgesia. These changes peaked about 1 week after nerve surgery and lasted 4–6 weeks in the CCI model and more than 8 weeks in the SNI model.

### Effects of DC lesions

Selective bilateral DC lesions, at upper cervical level, produced significant reduction of the mechanical and cold allodynia and the heat hyperalgesia in both models of mononeuropathy. As illustrated in Figs. 2 and 3, the mechanical allodynia was abolished following the DC lesion performed 2 weeks after the induction of mononeuropathy in both animal models. This was shown by a significant decrease of the mechanical allodynia assessed by the number of PWs in response to stimulation with Von Frey hairs, which returned to the basal levels observed before the induction of the mononeuropathy.

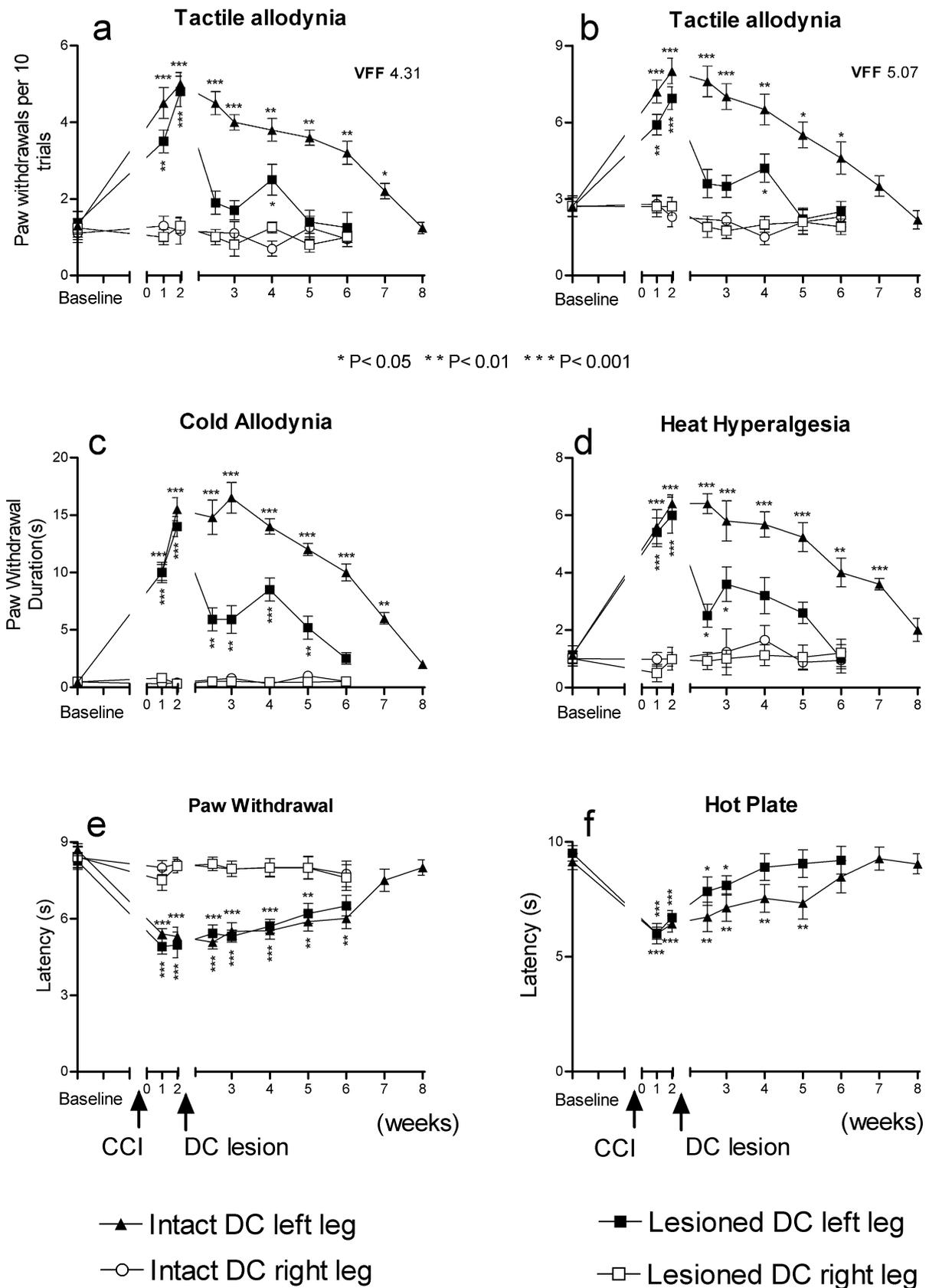


Fig. 2. Bilateral DC lesions altered the development of neuropathic manifestations in rats subjected to CCI mononeuropathy. Two groups of rats ( $n = 7$  each) were subjected to CCI mononeuropathy. Two weeks later, bilateral DC lesion was performed on one of these groups. Each point in each curve corresponds to the average  $\pm$  S.E.M. measurements performed on a group of rats at the indicated time interval. The degree of significance of differences was measured with reference to baseline measurements performed on the same animals before any surgical procedures.

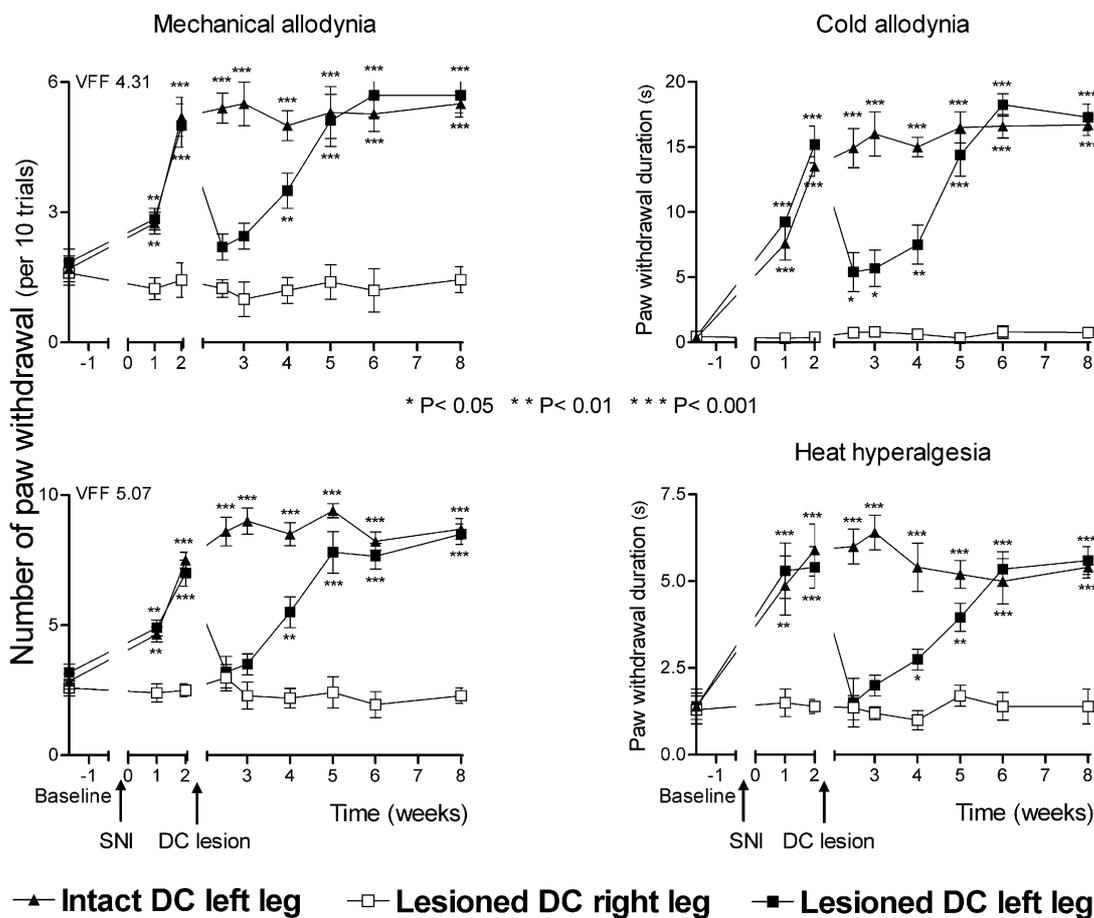


Fig. 3. Bilateral DC lesions produced transient alteration in the development of neuropathic manifestation in rats subjected to SNI mononeuropathy. Two groups of rats ( $n=7$  each) were subjected to SNI mononeuropathy. Two weeks later, bilateral DC lesion was performed on a group of rats at the indicated time interval. Each point in each curve corresponds to the average  $\pm$  S.E.M. measurements performed on a group of rats at the indicated time interval. The degree of significance of differences was measured with reference to baseline measurements performed on the same animals before any surgical procedures.

Simultaneously, the cold allodynia and the heat hyperalgesia were significantly reduced in both rat models.

The heat hyperalgesia, which was assessed by the PW and the HP latency tests, was evident only in the CCI model and showed an ambivalent reaction to the DC lesion. Unlike the PWL which remained reduced after the DC lesion, the HP latency elicited a significant trend to return to its values observed before the induction of neuropathy (Fig. 2e, f). The reduction of the neuropathic manifestations was maintained over an average period of 1–2 weeks in both models. After that period, the allodynia and hyperalgesia regained their levels before DC lesion in the SNI group (Fig. 3), while they almost disappeared in the CCI group (Fig. 2). It is worthy to note that mononeuropathy and DC lesions did not produce significant alterations in the sensory functions of the opposite (intact) legs (Figs. 2 and 3). Furthermore, unilateral (i.e. hemi) DC lesion on the opposite side of the neuropathic leg did not alter the manifestations of mononeuropathy in both models (Fig. 4).

#### Effect of timing of the DC lesion in the CCI model

The differences observed between the effects of the DC

lesion in the SNI and CCI models, may be related to differences in the duration of neuropathies in these models. For this reason, the sequence of execution of the CCI neuropathy and the DC lesion was changed in a second set of experiments. This change involved either reducing the time interval between the two procedures, or performing the bilateral DC lesions before the CCI mononeuropathy.

In a first attempt, CCI was performed on the second leg in rats previously subjected to neuropathy in a first (left) leg (followed by a bilateral DC lesion). Rats subjected to a second CCI developed allodynia and hyperalgesia comparable to that observed in rats with intact DC (Fig. 5). It is also important to note that the neuropathic manifestations appeared immediately and reached a maximum score within the first week following the nerve constriction (Fig. 5).

When the DC lesion was performed 3 days after the induction of CCI neuropathy, this procedure resulted in a moderate delaying of the onset of neuropathic manifestation and to a shortening of its time development as shown in Fig. 6.

The effects of DC lesions, simultaneous with or preceding the induction of mononeuropathy by 1 or 2 weeks,

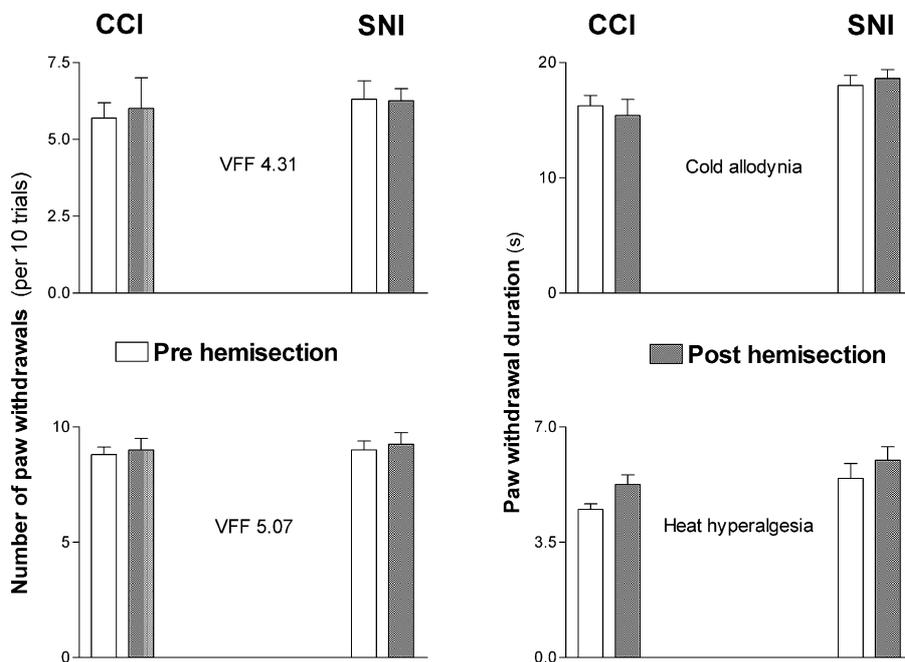


Fig. 4. Lesions to one side of the DCs (hemisection) contralateral to the neuropathic leg did not alter the neuropathic manifestations in rats subjected to either model of the mononeuropathy (two groups,  $n=5$  each). Each bar in each test corresponds to the average of measurements made either 2 weeks after the induction of mononeuropathy (pre-hemisection) or 1 week after one side DC lesion (post-hemisection).

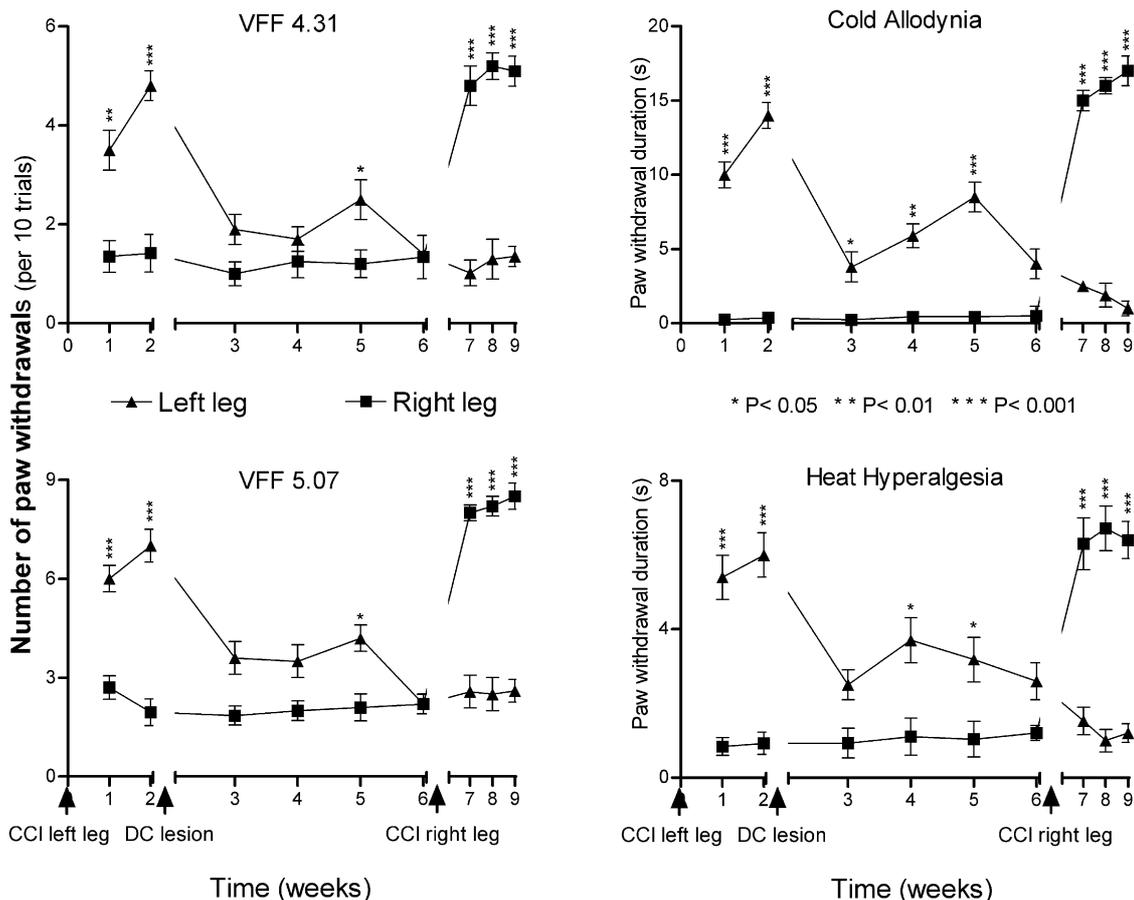


Fig. 5. Recurrence of neuropathic manifestations in rats subjected to CCI following chronic DCs lesion. Rats ( $n=7$ ) were subjected to CCI in the left leg followed, 2 weeks later, by bilateral DC lesion. Then after 6 weeks, the same rats received CCI on their right legs. Each point in each curve corresponds to the average of measurements made on all animals during the corresponding time interval. The significance of differences was calculated for the values measured on one leg in comparison to those observed on the opposite leg for the same time interval.

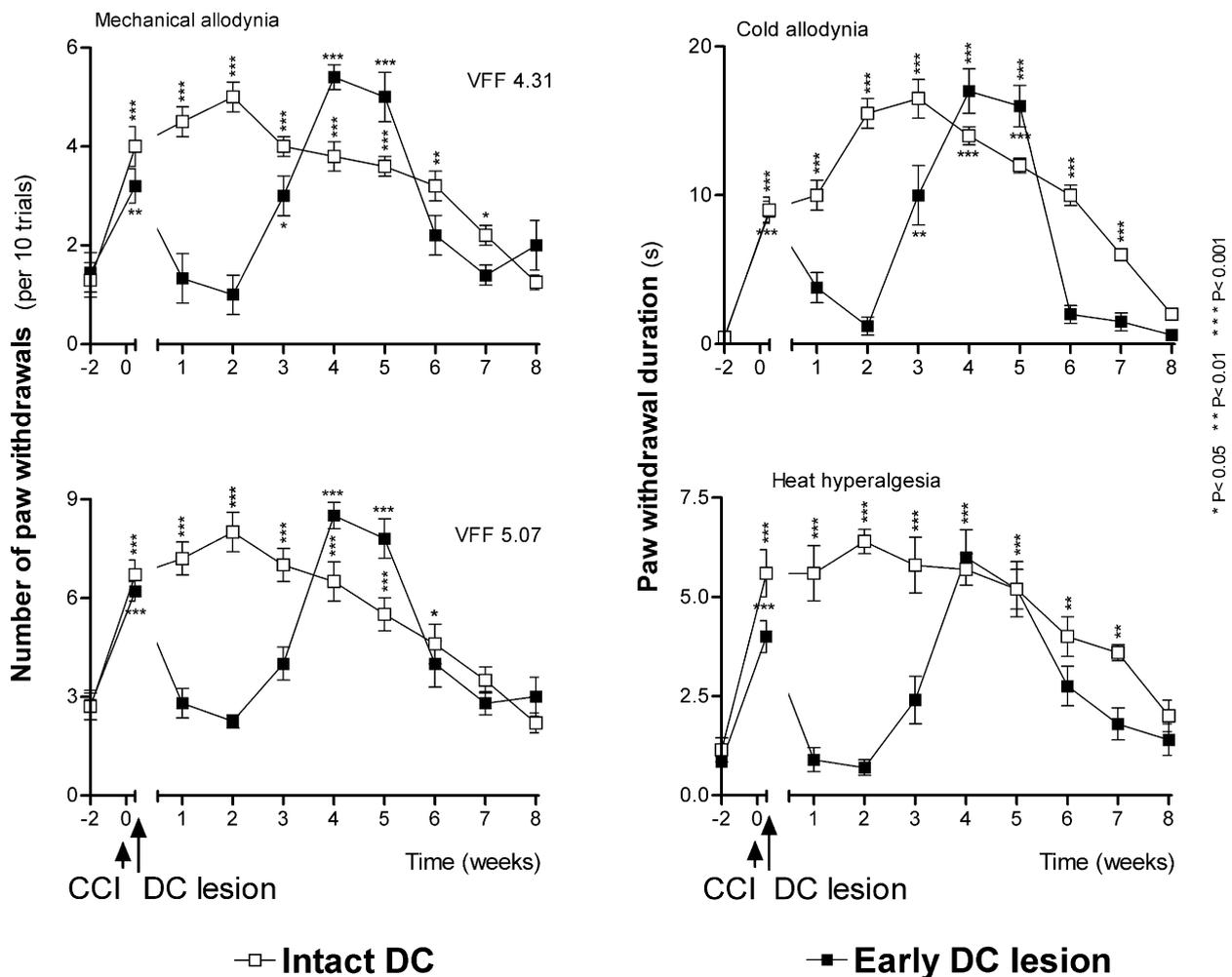


Fig. 6. Bilateral DC lesions, during the first week following CCI, delayed but did not prevent the full expression of neuropathic manifestations. DC lesion was performed at day 3 following CCI in one group ( $n=7$ ) of rats. The second group ( $n=7$ ) was subjected to CCI, without spinal lesions. The effects are compared, for the test of significance of differences, to the baseline established before the induction of neuropathy.

were tested on three different groups of rats (as one group per time interval). Figure 7 shows that simultaneous DC lesion and CCI delayed the onset of neuropathic manifestation for about one week, while the remaining two groups developed regular neuropathic manifestations that reached their maximum within 1 week following the nerve injury and disappeared after an average time of 6 weeks.

#### DISCUSSION

Following peripheral nerve injuries, functional and structural changes have been reported in the affected and neighboring nerve fibers (reviewed by Devor and Seltzer, 1999). At central levels, these changes result in sprouting of the A $\beta$  fibers to the superficial laminae of the dorsal horn known to be involved in the processing of nociceptive information (Woolf et al., 1995; Bester et al., 2000; Kohama et al., 2000), in expression of substance P receptors by neurons located in laminae

III–IV (Abbadie et al., 1997; Honore et al., 1999) which normally respond to innocuous inputs, in increased neuronal activities and substance P expression in the DC nuclei (Noguchi et al., 1995) and in thalamic hyperexcitability (Guilbaud et al., 1990; Miki et al., 2000). Peripheral and central changes, taken together, suggest that the DC system could be involved in the processing of the altered somatic sensory information during neuropathic conditions. Moreover, recent studies have provided more direct evidences about the involvement of the DC in rostral transmission of neuropathic manifestations. Using the spinal nerve ligation (SNL) model (Kim and Chung, 1992), spinal lesions at mid-thoracic levels have been shown to abolish tactile allodynia without altering thermal hyperalgesia (Bian et al., 1998; Sung et al., 1998). Further investigations showed that tactile allodynia is transmitted through the DC pathway (Sun et al., 2001) and reported increased activities of the gracile neurons ipsilateral to the neuropathic leg (Miki et al., 1998), while selective lesion of the DCs have been shown to alter the neuronal firing in the con-

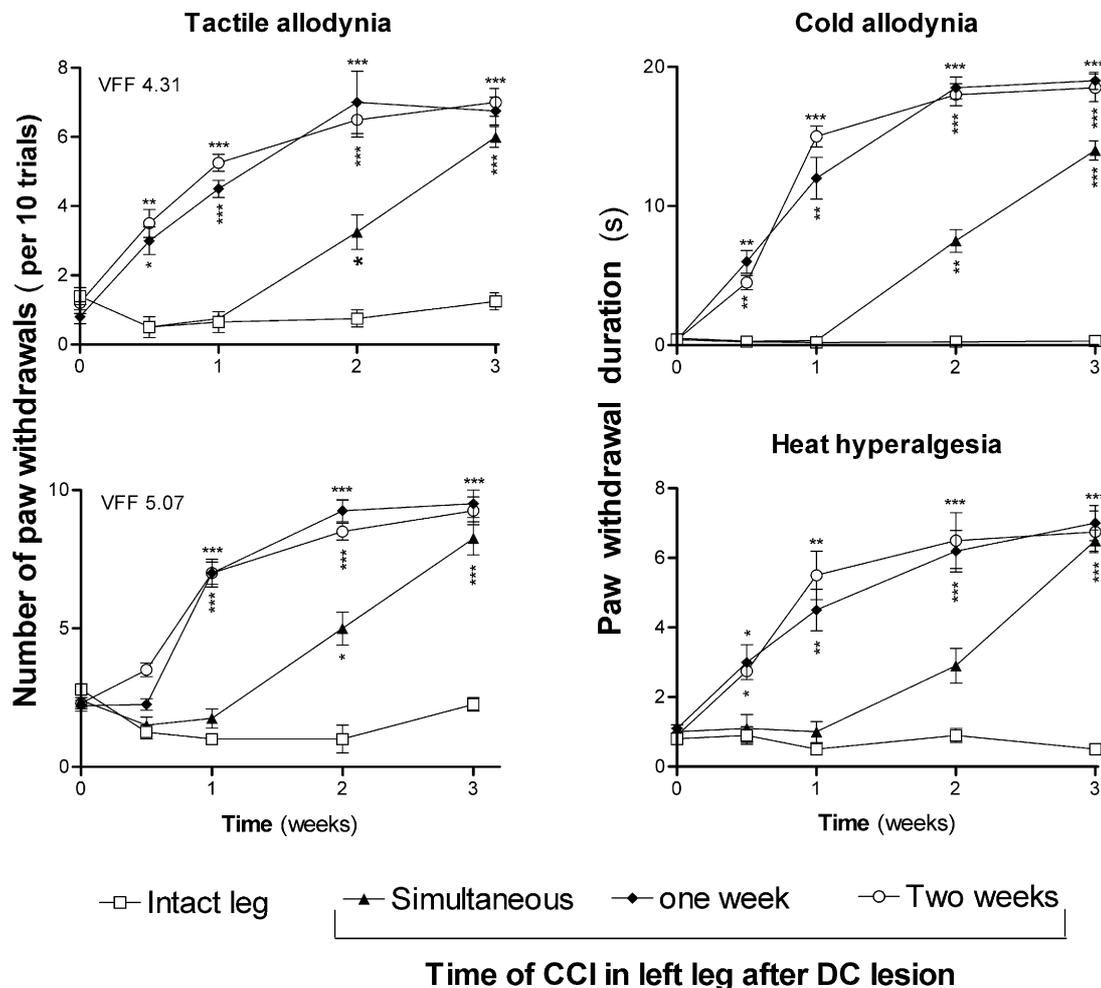


Fig. 7. DC lesions performed simultaneous with or before CCI did not prevent neuropathic manifestations. Three groups of rats ( $n=5$  each) were subjected to CCI either at the same time or 1 or 2 weeks following bilateral DC lesion. The trace of intact leg represents the average measurements made on all three groups of rats. The time zero in each panel corresponds to that of the induction of neuropathy for the three groups. The values on the Y-axis at time 0 correspond to baseline measurements made on rats before the induction of neuropathy and after DC lesion.

tralateral thalamic ventrobasal complex (Miki et al., 2000).

Further evidence supporting the hypothesis of segregation of neuronal pathways responsible for the transmission of tactile allodynia and heat hyperalgesia comes from the studies of Shir and Seltzer (1990) who showed the loss of heat hyperalgesia in the CCI model performed on rats neonatally treated with capsaicin, and of Ossipov et al. (1999) who showed that blocking the C fibers by the potent capsaicin analogue, resiniferatoxin, reduced the thermal hyperalgesia without altering the tactile allodynia in rats subjected to SNL neuropathy.

The present study used two different models for the induction of mononeuropathy in rats. In the first model (Bennett and Xie, 1988), the method of CCI of the sciatic nerve has been shown to produce total degeneration of myelinated fibers and significant changes in the unmyelinated fibers (Gautron et al., 1990; Basbaum et al., 1991; Carlton et al., 1991). Therefore, the involvement of the DC in neuropathic manifestation in this model is expected to be indirect, because of the degeneration of

their peripheral terminations except for those in the remaining saphenous nerve and supplying the medial aspect of the leg (Woolf et al., 1995). In the SNI model (Decosterd and Woolf, 2000), the intact myelinated and unmyelinated fibers in the sural and the saphenous nerves are affected by the injury to the other nerves supplying the leg (Liu et al., 2000; Wu et al., 2001); consequently, the DC system is a more likely candidate to be directly involved in the neuropathic manifestations, because it contains the ascending branches of the A $\beta$  fibers activated by probing the neuropathic leg.

The results of this study confirm further the contribution of the DC system in neuropathic manifestations and unravel several new aspects about this involvement. Firstly, DC lesion resulted in equal reduction of tactile and cold allodynias in addition to thermal hyperalgesia in both models used (Fig. 8) which suggests a possible direct or indirect involvement of the DC system in the processing of all neuropathic manifestations. Secondly, the lack of effect of DC lesion on the PWL test in the CCI model is not enough evidence about its incapacity to

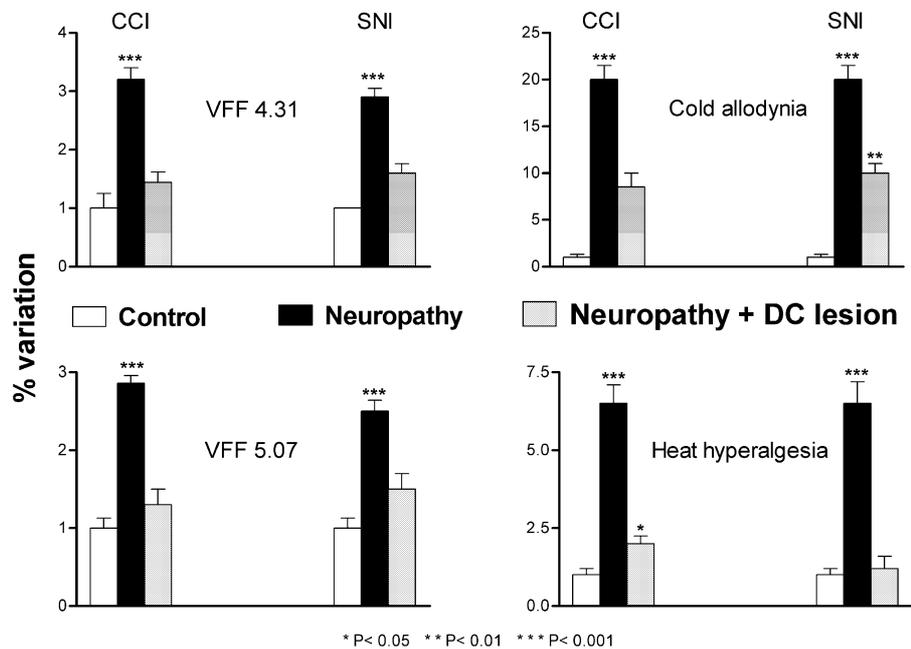


Fig. 8. Bilateral DC lesions exerted equal effects on the various tests of neuropathies in both animal models of mononeuropathy. Each bar in each panel represents the average of measurements performed in one animal group ( $n=7$ ) for each animal model before (control) and 2 weeks after the induction of neuropathy which was followed 2 weeks later by bilateral DC lesion.

influence thermal hyperalgesia. In fact, the latency of one of the two tests used to assess the thermal hyperalgesia, the HP test, was affected by the DC lesion (Fig. 1F). The main difference between the HP and the PW tests is that the former is coordinated supraspinally, while the latter can be observed in spinal animals. Therefore, this nuance in the effects of the DC on neuropathic thermal hyperalgesia, provides further evidence about its role in rostral transmission of neuropathic manifestations. Thirdly, the disturbed heat thermoception was not evident by the variations of the latency of the PW test in the SNI model, but was observed from the monitoring of the PWD in response to nociceptive heat in both the CCI and SNI models. This increased reaction to heat (or hypersensitivity) was significantly and equally reduced by selective DC lesions in both animal models for neuropathy (Fig. 8). Fourthly, selective DC hemilesion, contralateral to the injured leg, did not produce any of the reported signs of DC lesion involving the ascending fibers on the side ipsilateral to the neuropathic leg which could be directly or indirectly involved by the peripheral nerve injury.

The reduction of all the neuropathic manifestations, in both the CCI and SNI models, by DC lesion could not be exclusively attributed to a simple interruption of a pathway for rostral transmission. In fact the DC lesion can lead to one or more of the following consequences: firstly, the interruption of rostral transmission in this system and the resulting changes, known as deafferentation syndrome, in the functions of the brain centers receiving its influence; secondly, the interruption of a descending pathway projecting from the DC nuclei to the dorsal horn (Bromberg et al., 1981) (although the function of this secondary pathway or tract is not well

established, its interruption can lead to the failure of a circuit, possibly reverberating, established between the dorsal horn and the DC nuclei); thirdly, the induction of trophic changes that may affect retrogradely the function of the cell bodies and the other ramifications of the same afferent neurons.

Trophic changes appear to constitute a major factor in the reported effects of the DC lesions. This assumption is supported by several direct and indirect observations on the outcome of injuries to peripheral and central terminations of sensory neurons. In fact, the reversibility or persistence of neuropathic manifestations in the described animal models, depend to a large extent on the ability of the peripheral processes of sensory neurons to regenerate and find their original targets. This is shown by the extinction of neuropathic manifestations within a few weeks in the CCI model or the dependence of their persistence on the type of injury used in the SNI model (reversibility within weeks with the use of compression on the peripheral nerves, and persistence over weeks and months after ligations and cutting of nerves, Decosterd and Woolf, 2000). Long-term experimental observations on the effects of injury to central processes of sensory neurons are not available, since all the reports on the effects of selective or total spinal lesions on neuropathic manifestations have been restricted to the immediate observations made within few hours or days after the lesion.

Previous work from our laboratory has provided evidence for a critical role of the timing of injuries to the peripheral and central terminations of sensory neurons on the autotomy behavior in rats. This study has shown that simultaneous lesion of the sciatic and saphenous nerves with the DC tracts elicits early and massive autot-

omy in rats which was labeled explosive autotomy (Saadé et al., 1993), while time intervals in days or weeks between the peripheral and central injuries failed to elicit significant alterations in the time course of the autotomy behavior in rats as initially described by Wall et al. (1979). This early observation on the importance of the effects of timing of injuries led to two assumptions to explain the reported effects of DC lesion in the first set of experiments (Figs. 2 and 3). Firstly, the observed differences in the recurrence of neuropathic manifestations between the CCI and SNI models may be related to the reversibility and persistence of those symptoms in the two models (reversibility within 6–8 weeks in the CCI model, and persistence over weeks and months in the SNI model). Secondly, the reduction of neuropathic manifestations in the two models may be attributed to discrete plastic changes induced by the lesion of the central processes of the sensory neurons in the DC system. The reported results of the variations of the time interval between the DC lesion and induction of neuropathy, demonstrate that the effects of DC lesion disappear after an average period of 1–2 weeks. Therefore, the time span of inhibition of neuropathic manifestation by lesions to the central processes of afferent neurons mirrors the time to peak of these manifestations after lesion of the peripheral processes of the same neurons. Several research reports have been devoted to peripheral and central plastic changes induced by lesions to the peripheral sensory axons (for reviews see Woolf, 1997; Devor and Seltzer, 1999). In contrast, reports on the short- and long-term effects of lesions of central axons are not as abundant and describe essentially the clinical observations collected from surgical lesions of tracts for the relief from chronic pains.

A major implication of the above-mentioned observations is that the DC system, under neuropathic conditions, can behave like the lateral spinothalamic tract, as a system for transmission of mechanical and thermal nociceptive information. Nociceptive signaling through the DC, during pathological states, has also been reported following strokes (Triggs and Beric, 1994) and injuries to the CNS (Beric, 1997).

The recurrence of all the neuropathic manifestations, 1 or 2 weeks following the DC lesion, provides evidence about the flexibility of the plastic changes induced by injuries to the peripheral nervous system. This observation provides further evidence against the concept of specificity of the pathways subserving neuropathic pains and may be correlated with the clinical experience of the long-term failure of anterolateral cordotomies (Nathan and Smith, 1979), where the original pain recurs within 3–6 months after cordotomy.

Finally, the experimental data gathered from this study allow the following main conclusions; firstly, the classical description of the neuronal pathways involved in the processing of acute nociception does not apply to the transmission of chronic (neuropathic) pain. Secondly, injuries to the nervous system can induce plastic changes (peripheral and/or central) that can explain some puzzling features of chronic pains and their recurrence following either pharmacological or surgical treatments.

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