Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli

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Summary
Studies in healthy volunteers suggested that the classical counterirritation phenomenon (i.e. pain inhibits pain effect) might depend on diffuse noxious inhibitory controls (DNIC), which modulate the spinal transmission of nociceptive signals. In the present study, we sought to determine whether similar mechanisms were at play in patients with different subtypes of neuropathic pain. Ten patients presenting with a traumatic peripheral nerve injury associated with dynamic mechano-allodynia (i.e. pain triggered by brushing) or static mechano-allodynia (i.e. pain triggered by light pressure stimuli) were included in this study. To investigate counterirritation mechanisms in these patients, we analysed the RIII nociceptive flexion reflex and concomitant painful sensation elicited by electrical stimulation of the sural nerve. We compared the effects of heterotopic ‘clinical’ conditioning stimuli (i.e. pain evoked by brushing or pressure within the allodynic area located in the upper limb or chest) to those of experimental heterotopic noxious stimuli (HNCS) consisting of a cold pressor test or tourniquet test applied to the normal upper limb. Static mechano-allodynia induced inhibitions of both the RIII reflex and the concomitant painful sensation. These effects were similar to those induced by HNCS and were probably due to an increased activation of DNIC. In contrast, in patients with dynamic allodynia, brushing within the allodynic area reduced the pain sensation at the foot, but did not inhibit the electrophysiological responses, suggesting that in this case the counterirritation effect may take place at the supraspinal level. Thus, the mechanisms of counterirritation are not univocal, but depend on the pathophysiological mechanisms of clinical pain.

Keywords: nociceptive reflex; neuropathic pain; allodynia; pain modulation; electrophysiology

Abbreviations: DNIC = diffuse noxious inhibitory controls; HNCS = heterotopic noxious conditioning stimuli; VAS = visual analogue scale; WDR = wide dynamic range

Introduction
The negative interaction between pain sensations elicited concomitantly by two remote sources of noxious stimuli is a classical clinical observation that has constituted the basis for a variety of analgesic procedures (Wand-Tetley, 1956). In accordance with these observations, psychophysical studies in healthy volunteers have confirmed that various experimental noxious conditioning stimuli (e.g. thermal, mechanical, electrical) reduce the perception of pain due to a test stimulus (Hardy et al., 1940; Gammon and Starr, 1941; Pertovaara et al., 1982; Talbot et al., 1987; Price and McHaffie, 1988). Complementary studies in animals and humans have suggested that such a ‘pain inhibits pain’ effect, also referred to as ‘counterirritation’ phenomenon, depends on specific neurophysiological mechanisms involving endogenous modulatory systems of the spinal transmission of nociceptive signals. In animals, the activity of spinal dorsal horn wide dynamic range neurons is inhibited selectively and powerfully by the application of noxious stimuli to any part of the body distant from the neurons’ excitatory receptive field (Le Bars et al., 1979a, b). In humans, the spinal nociceptive flexion reflex (RIII)—whose threshold and amplitude are closely related to those of subjective pain perception (Willer, 1977)—is inhibited in an intensity dependent manner by heterotopic (i.e. extrasegmental) painful stimuli (Willer et al.,...
1984). Such inhibitory effects, which have been termed diffuse noxious inhibitory controls (DNIC), are subserved by an anatomical spino-bulbo-spinal loop (see references in Discussion).

The studies performed in healthy volunteers evidenced a clear relationship between the nociceptive nature (i.e. high intensity) of the conditioning stimulus and inhibitions of the perception or electrophysiological responses associated with the test stimulus. However, the mechanisms of counter-irritation elicited by clinical pain remain uncertain, as the relationship between the stimulus intensity and the resulting sensation is significantly modified under pathological conditions by the reorganization and alterations of the nociceptive systems (Dubner and Gold, 1999; Julius and Basbaum, 2001; Woolf and Salter, 2000).

The aim of the present study was to investigate the pain inhibiting effects induced by allodynia. This symptom, which is frequently (but not specifically) observed in patients with peripheral nerve injury, represents a special case of clinical pain since it is elicited by stimuli that normally do not provoke pain. In other words, allodynia could be considered as a painful sensation due to non-nociceptive stimuli. Using a similar paradigm to that used in healthy volunteers, we compared the effects of heterotopic (i.e. extrasegmental) allodynic and experimental pains on both the RIII nociceptive flexion reflex and the concomitant painful sensation. Patients selected for this study presented with a peripheral nerve injury associated with dynamic or static mechano-allodynia. These two subtypes of mechanical allodynia, triggered either by brushing or light pressure stimuli, involve different peripheral (and probably central) pathophysiological mechanisms (Koltzenburg et al., 1992, 1994; Ochoa and Yarnitzki, 1993). Brush-evoked pain (i.e. dynamic mechano-allodynia) is mediated by large myelinated peripheral fibres, while pain elicited by light pressure stimuli (i.e. static mechano-allodynia) is mediated by fine (nociceptive) afferent fibres. Thus, these clinical conditions represented unique ‘models’ for comparing the pain suppressive effects of painful nociceptive stimuli with those of painful but non-nociceptive stimuli.

Methods

Patients

Thirteen patients suffering from pain due to a traumatic peripheral nerve injury were recruited consecutively and gave informed written consent. The study was approved by the Local Ethical Committee (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, CCPPRB, Hôpital Ambroise Paré).

Each patient underwent a complete neurological examination. Intensity of pain was assessed using a 100 mm visual analogue scale (VAS) graduated from 0 (no pain) to 100 (worst possible pain).

The inclusion criterion was the presence of a static and/or dynamic mechano-allodynia with a location that could be clearly attributed to the peripheral nerve injury. Dynamic mechano-allodynia was considered to be present if stroking the skin evoked a clear sensation of pain (i.e. VAS score >40 out of 100). Static mechano-allodynia was considered to be present when a clear sensation of pain (i.e. VAS score >40 out of 100) was evoked by light pressure stimuli, which did not evoke painful sensations when applied on the contralateral side.

The exclusion criteria were: pains other than the neuropathic pain; severe depression; pregnancy; chronic alcoholism or substance abuse; any mental disorders preventing an accurate understanding of the tests; and participation in another protocol.

Nociceptive flexion reflex (RIII reflex)

The RIII reflex was elicited and recorded from the lower limb according to a previously described and validated technique (Willer, 1977; Willer et al., 1984, 1989). During the recordings, the subjects sat comfortably reclined in order to ensure a state of complete muscular relaxation. The RIII reflex was elicited and recorded by an entirely computerized system (Physio Labo System, Notocord, Croissy, France, www.notocord.com). The sural nerve was electrically stimulated at a frequency of 0.17 Hz (10 stimulations per min) via a pair of surface electrodes placed 2 cm apart on the degreased skin overlying the nerve within its retromalleolar path. Each electrical stimulation consisted of a train of five constant current pulses of 1 ms duration. Electromyographic responses were recorded from the ipsilateral biceps femoris via a pair of surface electrodes placed 2 cm apart on the degreased skin over the muscle. The RIII reflex response was identified as a multiphasic signal appearing between 90 and 180 ms after each stimulation. After amplification, each reflex response was digitized, full-wave rectified and integrated. This integrated surface was used to quantify the RIII response. The RIII reflex threshold was defined as the average minimal current that elicited the reflex response. Before each experiment, this threshold was determined by four successive sequences of increasing and decreasing electrical stimuli. Such stimuli elicited slightly painful sensations of the pinprick type, which were described by the subjects as originating from the stimulating electrodes and projecting into the distal cutaneous receptive field of the sural nerve on the lateral side of the foot. The intensity of electrical stimulation of the sural nerve was then adjusted to 20% above the threshold and kept constant during control, conditioning and post-conditioning periods of each experimental sequence.

Conditioning stimuli

‘Clinical’ conditioning stimuli consisted of brushing or pressure mechanical stimuli applied within the allodynic area or the contralateral non-painful area. In patients with dynamic allodynia, tactile stimuli were performed with a
brush (frequency of stimulation: one stroke per second). In patients with static allodynia, pressure stimuli were performed by means of a pressure algometer (Somedic Sales AB, Stockholm, Sweden), which enabled the control and quantification of the intensity (in kPa) of each stimulus (area of stimulation: 1 cm²). Before conditioning, pressure pain thresholds were measured on both the normal and allodynic sides according to the method of limits (Jensen et al., 1986). In order to induce a constant and tolerable level of pain, the intensity of stimulation during conditioning was adjusted between 15 and 20% above the pressure pain threshold measured on the allodynic side.

Experimental conditioning heterotopic noxious stimuli consisted of the cold pressor test or tourniquet test applied on the normal upper limb. These two experimental stimuli were chosen since previous studies in healthy volunteers have shown that they induce strong inhibitions of both the RIII reflex and simultaneous sensations (Willer et al., 1984). During the cold pressor test, the patients immersed the entire normal hand in a circulating water bath at 2–4°C. During the tourniquet test, the patients performed a 10 watts muscular exercise with the left forearm during ischaemic blocking of the arterial blood flow produced by a pneumatic cuff placed around the middle of the arm and inflated to 1.5 × the systolic blood pressure.

**Experimental design**

Each individual experiment started with a control period during which the application of a stimulus at an intensity adjusted to 20% above the threshold of the RIII reflex resulted in stable reflex responses. This preliminary finding was regarded as a prerequisite before starting the conditioning procedure.

Three experimental sequences were performed in patients with dynamic or static mechano-allodynia in order to test:

(i) The effects of brushing or pressure stimuli applied within the allodynic area;

(ii) The effects of the same stimuli applied on the contralateral homologous non-painful side;

(iii) The effects of noxious stimuli (i.e. noxious cold or tourniquet test) applied on the normal upper limb.

**Table 1 Clinical and demographic characteristics of the patients who completed the study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Site of lesion</th>
<th>Type of allodynia</th>
<th>Duration of allodynia (months)</th>
<th>Spontaneous pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>46</td>
<td>L median</td>
<td>Static</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>L ulnar</td>
<td>Static</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>55</td>
<td>L ulnar</td>
<td>Static/dynamic</td>
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<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>59</td>
<td>R ulnar</td>
<td>Static</td>
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<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>35</td>
<td>R musc.cutaneous</td>
<td>Static/dynamic</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>L ulnar</td>
<td>Static</td>
<td>35</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>26</td>
<td>R intercostal</td>
<td>Dynamic</td>
<td>22</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>68</td>
<td>R ulnar</td>
<td>Dynamic</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>31</td>
<td>L radial</td>
<td>Dynamic</td>
<td>23</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>36</td>
<td>R ulnar</td>
<td>Dynamic</td>
<td>12</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Fig. 1** Individual example of the effects of heterotopic light pressure conditioning stimuli applied on the alldynic (A, B) or contralateral side (C, D) on the RIII reflex recorded from the lower limb and concomitant sensation, in a patient presenting with static allodynia. Application of the conditioning stimuli on the alldynic side was painful (VAS score: 73) and induced inhibitions of both the RIII reflex (A) and concomitant sensation (B). Application of the same conditioning stimuli on the contralateral normal side was not painful (VAS score: 0) and did not alter the reflex responses (C) or the concomitant sensation (D). In (A) and (C), each bar represents a single reflex response, expressed as a percentage of the mean value for the 2-min pre-conditioning control period. The 1-min conditioning period is indicated by arrows.

Two additional experimental sequences were performed in the patients presenting with both static and dynamic allodynia, since the effects of brushing and pressure stimuli were tested on both sides. The order of application of the conditioning stimuli was randomized.
Each experimental sequence lasted 5 min and included a 2-min control period, 1 min of heterotopic stimulation, and a 2-min period to analyse the aftereffects. Painful sensations due to the electrical stimuli were quantified on a VAS before application of the conditioning stimulus. At the end of each conditioning stimulation, the patients were asked to quantify the painful sensations evoked by both the conditioning and test stimuli (i.e. RIII reflex). Finally, the patients were asked to rate the painful sensations due to electrical stimulation 1 and 2 min after the conditioning.

**Statistical analysis**

Results were expressed as means ± SD. To allow analysis of group data, the RIII responses were averaged at 1-min intervals and expressed as a percentage of the mean control value. Statistical analysis of RIII inhibition was performed by two-way analysis of variance (ANOVA), with the Fischer’s post hoc least significant difference test. Wilcoxon’s Signed Ranked test and the Mann–Whitney test were used for comparison of paired and unpaired data.

**Results**

Ten patients (six males, four females, mean age: 42 ± 14 years) presenting with dynamic and/or static mechanio-allodynia due to a traumatic nerve injury completed the study (see Table 1). Four patients presented with a dynamic allodynia only, four patients presented with static allodynia only and two patients presented with both types of allodynia within the same nerve territory. The allodynic areas were localized in the territories of the ulnar (n = 6), median (n = 1), radial (n = 1), musculocutaneous (n = 1) or intercostal nerves (n = 1). The mean duration of allodynia was 30 ± 16 months. In six patients, allodynia was associated with spontaneous ongoing pain with a burning quality (mean VAS score 66.6 ± 9.6).

Three patients were excluded because they did not tolerate the electrical stimuli (n = 2) or because of a lack of stability of the reflex responses (n = 1).

**Effects of heterotopic ‘clinical’ painful stimulation on the RIII reflex and concomitant sensation**

The RIII reflex threshold was similar in patients presenting with static or dynamic allodynia (7.1 ± 2.3 and 7.4 ± 1.8 mA).

In patients with static allodynia, the pressure pain threshold was significantly lower on the allodynic side than on the contralateral homologous nonpainful side (76.3 ± 28.7 and 384.0 ± 37.5 kPa, respectively; P < 0.01). ‘Clinical’ conditioning stimuli consisting of light pressure stimuli...
individual example and in Fig. 4 with the cumulated data, the RIII reflex responses were not altered significantly during such conditioning stimuli (Fig. 4A). In contrast, a significant reduction of the concomitant painful sensation was observed during the conditioning (59.2 ± 12.3% of control values; P < 0.01) (Fig. 4B). This inhibition of the sensation evoked by electrical stimuli of the sural nerve was not significantly different from that observed in patients with static allodynia. However, its time course was clearly different between the two groups of patients, since in patients with dynamic allodynia, inhibitions of the sensation did not outlast the 1 min duration of the conditioning. Application of stroking on the contralateral homologous side was not painful and did not induce a significant change of the reflex responses or concomitant painful sensation (Fig. 4C and D).

The differential effects of static and dynamic allodynia on the RIII reflex and sensation are further illustrated by the results observed in the two patients presenting with both types of allodynia. Light pressure applied to the alldyinic area induced inhibitions of both the RIII reflex and concomitant painful sensation (Fig. 5A and B). In contrast, stroking within the same nerve territory, which elicited a similar level of pain, induced a reduction of the painful sensation due to electrical stimulation of the sural nerve but no modification of the RIII reflex (Fig. 5C and D).

**Effects of heterotopic noxious conditioning stimuli on the RIII reflex and the concomitant sensation**

The experimental heterotopic noxious conditioning stimulation (HNCS) consisted of a cold pressor test in all patients but two (one with static and one with dynamic allodynia) who did not tolerate this test. In these two patients, the HNCS consisted of the tourniquet test.

The intensity of pain elicited by HNCS was similar in patients with static or dynamic allodynia (mean VAS score: 71.0 ± 14.6 and 71.7 ± 8.4, respectively). As illustrated in Fig. 6, HNCS induced inhibitions of both the RIII reflex responses and the concomitant painful sensation in patients presenting with static or dynamic allodynia. Inhibitions of the RIII reflex (55.5 ± 15.0% and 57.8 ± 12.5% of control values) and of the concomitant painful sensation (60.3 ± 13.6% and 55.8 ± 14.6% of control values) were not significantly different between the two groups of patients. In both groups of patients, the inhibitory effects outlasted the conditioning stimulation by one minute.

**Comparison of the effects of clinical and experimental conditioning stimuli in patients presenting with a static or dynamic mechano-allodynia**

In patients with static mechano-allodynia, experimental (i.e. HNCS) and clinical (i.e. light pressure) conditioning stimuli...
elicited a similar level of pain (mean VAS score: 71 ± 14.6 and 72.6 ± 10.3). The effects of the two types of conditioning stimuli were similar as regards both the inhibitions of the RIII reflex responses (55.5 ± 15.0% and 58.2 ± 11.6% of control values) and concomitant sensation (60.3 ± 13.6 and 56.0 ± 13.8% of control values). Moreover, the time course of the inhibitory effects elicited by the two types of stimuli was similar since, in both cases, it outlasted the period of conditioning by 1 min.

In patients with dynamic alldynia, experimental (i.e. HNCS) and clinical (i.e. brushing) conditioning stimuli elicited a similar level of pain (mean VAS score: 71.7 ± 8.4 and 74.8 ± 11.4, respectively). Both types of stimuli induced similar inhibitions of the painful sensation associated with electrical stimulations of the sural nerve (55.8 ± 14.6% and 59.3 ± 12.3% of control values, respectively). However, the time course of the inhibitions was different since inhibitions elicited by HNCS outlasted the period of stimulation, but not those elicited by the clinical conditioning. In addition, the effects of experimental and clinical conditioning on the electrophysiological responses were clearly different ($P < 0.001$) in these patients, since inhibitions were observed during experimental, but not clinical (i.e. brushing) conditioning stimulation.

Finally, in an attempt to determine whether counterirritation could be triggered by spontaneous ongoing pain, we compared the RIII reflex threshold and concomitant sensation between patients with or without spontaneous pain. We found that the RIII reflex threshold (7.6 ± 2.4 and 7.2 ± 1.7 mA) and the concomitant painful sensation (mean VAS score observed during the control periods: 44.3 ± 8.2 and 44.6 ± 8.7) were not significantly different between the two subgroups of patients.

**Discussion**

The pain suppressive effect (i.e. counterirritation phenomenon) elicited by experimental or clinical painful heterotopic conditioning stimuli was compared in patients presenting with pathological pains triggered by light pressure or tactile stimuli (i.e. static and/or dynamic mechanical alldynia). The test stimulus consisted of recordings of the RIII nociceptive flexion reflex and the concomitant sensation elicited by electrical stimulation of the sural nerve to determine whether the inhibition of pain perception was associated with a reduction of the spinal transmission of nociceptive signals (presumably through activation of DNIC. We evidenced differential effects of the experimental and alldynic cond-
conditioning stimuli are inhibited in an intensity-dependent and long-lasting manner when conditioning nociceptive stimuli are applied to heterotopic areas of the body (Le Bars et al., 1979a, b; Dickenson et al., 1983; Villanueva and Le Bars, 1985; Morton et al., 1987; Ness and Gebhart, 1991). In man, heterotopic noxious stimuli inhibit the spinal nociceptive flexion (RIII) reflex, which reflects the spinal transmission of nociceptive signals (Willer et al., 1984, 1989; Terkelsen et al., 2001). In both animals and humans, these phenomena are sustained by a spino-bulbo-spinal loop with an ascending part located in the anterolateral quadrant of the spinal cord (Villanueva et al., 1986; Roby-Brami et al., 1987; De Broucker et al., 1990; Bouhassira et al., 1990, 1992, 1993a, b, 1995).

The present results indicate that, under pathological conditions, DNIC can be activated by normally non-painful stimuli. This is in accordance with the results of Willer et al. (1987) in patients with radicular pain and those of recent electrophysiological studies in animal models of inflammation or peripheral nerve injury (Danziger et al., 1999, 2001). In fact, we showed in neuropathic rats that the C-fibre evoked responses of trigeminal WDR neurons were inhibited by light pressure stimuli applied to the injured hind paw but not to the contralateral one. Such inhibitory effects were not due to central alterations of the DNIC circuitry, but to an increased activation of these inhibitory controls due to peripheral mechanisms leading to hyperexcitability (i.e. sensitization) of thin myelinated (Aδ) and unmyelinated (C) fibres which specifically trigger DNIC (Bouhassira et al., 1987). Such a sensitization of nociceptors to mechanical stimulation has been demonstrated in different animal models of neuropathic pain (e.g. Koltzenburg et al., 1994; Ahlgren et al., 1992; Tanner et al., 1998; Andrew and Greenspan, 1999).

The inhibitory effects induced by mild pressure observed in the patients with static allodynia might depend on similar mechanisms and involve an exacerbation of DNIC due to the sensitization of nociceptive afferents. In keeping with this hypothesis, it has been shown in patients with peripheral nerve injury that static allodynia was not altered during ischaemic nerve-compression blocking, suggesting that this symptom is mediated by fine afferents which are not affected by this type of differential nerve conduction blocking (Koltzenburg et al., 1992; Ochoa and Yarnitzki, 1993). In addition, hyperexcitability of C nociceptors was directly demonstrated by microneurographic recordings in a patient with a traumatic nerve injury who exhibited static allodynia (Cline et al., 1989).

Although they elicited a similar level of pain, experimental and clinical (i.e. brushing within the allodynic area), heterotopic conditioning stimuli induced differential effects in patients with dynamic mechano-allodynia. A reduction of the painful sensation evoked by electrical stimulation of the sural nerve was observed during both types of conditioning. However, the time course of the pain suppressive effects was different, suggesting differential neurophysiological mechanisms. Moreover, in these patients heterotopic noxious stimuli induced a clear inhibition of the RIII reflex whereas such an inhibition of the electrophysiological response did
not occur during the alldynic stimulation. The lack of inhibition of the nociceptive flexion reflex cannot be explained by specific alterations of the DNIC circuitry. Indeed, in these patients inhibitions of the RIII reflex induced by experimental noxious stimuli were similar to those observed in patients with static allodynia. Furthermore, inhibitions of the reflex were observed during pressure, but not brushing, within the alldynic area in patients presenting with both types of allodynia. Therefore, the dissociation of the effects on the sensory and electrophysiological responses indicates that the counterirritation phenomenon elicited by dynamic allodynia was not due to a reduction of the spinal transmission of nociceptive signals, but depended on other, probably supraspinal, mechanisms. Alternatively, one cannot formally exclude that the lack of effects of dynamic allodynia on the RIII reflex was due to a dissociated control from the spinal sensory neurons to the motoneurons.

The neurophysiological basis of dynamic allodynia is not fully understood. However, studies using reaction–time measurements, nerve compression–ischaemia–induced dissociated A-fibre blocking and transcutaneous electrical stimulation in patients with neuropathic pain of peripheral origin have shown that the dynamic subtype of mechanoallodynia is mediated by large myelinated afferent fibres (Campbell et al., 1988; Gracely et al., 1992; Price et al., 1989, 1992; Koltzenburg et al., 1992, 1994; Ochoa and Yarnitzki, 1993). Since these fibres normally encode non-painful tactile signals, it was concluded that brush-induced allodynia is due to central alterations in the processing of tactile stimuli. Several spinal mechanisms have been proposed (Woolf and Manion, 1999) including a loss of inhibitory mechanisms (Woolf and Wall, 1982; Sugimoto et al., 1990; Miletic and Miletic, 2000), sprouting of low threshold afferent endings into superficial layers of the dorsal horn of the spinal cord (Woolf et al., 1992, 1995; Shortland and Woolf, 1993; Koerber et al., 1994; Kohama et al., 2000) and functional alterations mediated notably by n-methyl-D-aspartate (NMDA) receptors (Woolf, 1983; Mao et al., 1992a,b; Malmberg et al., 1997) leading to the sensitization (i.e. hyperexcitability) of spinal neurons involved in pain transmission. In addition, a series of studies suggested that tactile allodynia involves supraspinal mechanisms. Spinal transections or inactivation of supraspinal structures such as the rostroventromedialmedulla or the periaqueductal grey can
suppress mechanical allodynia in animals with nerve injury (Pertovaara et al., 1996; Kauppila, 1997; Kauppila et al., 1998; Sung et al., 1998; Bian et al., 1998; Urban and Gebhart, 1999). Interestingly, recent data in neuropathic rats suggested that tactile allodynia is mediated through the dorsal columns and nucleus gracilis (Sun et al., 2001). Such a reorganization of the somatosensory systems, which remains to be demonstrated in humans, might explain the lack of activation of DNIC in patients with dynamic allodynia. Indeed, it has been demonstrated, in both animals and humans, that DNIC are mediated through ascending pathways confined to the anterolateral quadrant (Villanueva et al., 1986; De Broucker et al., 1990; Bouhassira et al., 1993b).

Another finding of the present study concerned the lack of electrophysiological or psychophysical effects of spontaneous ongoing pain. The fact that the threshold of the RIII nociceptive reflex and the concomitant sensation were similar in patients presenting with or without spontaneous ongoing pain suggests that this type of clinical pain is not able to trigger DNIC. These results are in accordance with those of previous studies showing that spontaneous pain of different aetiologies did not induce significant changes of the RIII reflex threshold (Boureau et al., 1991; Peters et al., 1992). However, it cannot be excluded that the level of spontaneous pain, which was inferior to that of allodynia, was not sufficient to trigger DNIC.

From a pathophysiologically point of view, the present data confirm that different neuronal populations are involved in the different components of neuropathic pain following nerve injury. Our results suggest that pressure allodynia is mediated through pathways involved in DNIC, while brush-induced allodynia and probably spontaneous ongoing pain result from abnormal central processing independent of those subserving DNIC. This leads to questioning of the pathophysiological role of DNIC. It has been suggested that DNIC might facilitate the integration of nociceptive information by the complementary processes of segmental excitation and diffuse inhibition of the spinal transmission of nociceptive signals (Le Bars et al., 1992). According to such a hypothesis, pathological pains would be associated with increased activation of DNIC. The results observed in the patients with static allodynia are compatible with such an interpretation. However, the results in the patients with spontaneous neuropathic pains or dynamic allodynia demonstrate that chronic pains are not always associated with a diffuse inhibition of spinal nociceptive processes.

In conclusion, the present data indicate that the mechanisms of the counterirritation phenomenon are not determined by the intensity or aetiology of the clinical pain, but by its pathophysiological mechanisms. DNIC might be involved in the case of pathological pains associated with a hyperactivation of the physiological nociceptive pathways, but not in the case of pains depending on more complex pathological alterations of the somatosensory systems.

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