Clinical Neurophysiology 123 (2012) 598–604

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Evoked potentials and quantitative thermal testing in spinal cord injury patients with chronic neuropathic pain

Hatice Kumru [a,*], Dolors Soler [a], Joan Vidal [a], Josep Maria Tormos [a], Alvaro Pascual-Leone [b], Josep Valls-Sole [c]

[a] Institut Guttmann Hospital de Neurorehabilitació–Institut Universitari adscript a la Universitat Autonoma de Barcelona, Barcelona, Spain
[b] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA
[c] EMG and Motor Control Unit, Neurology Department, Hospital Clínic, Universitat de Barcelona, IDIBAPS (Institut d'Investigació, Biomèdica August Pi i Sunyer), Spain

ARTICLE INFO

Article history:
Accepted 22 July 2011
Available online 17 August 2011

Keywords:
Spinal cord injury
Neuropathic pain
Evoked heat pain
Quantitative thermal testing
Evoked potential

HIGHLIGHTS

- Patients with spinal cord injury (SCI) and chronic neuropathic pain can demonstrate generalized pain perception changes at or above lesion level.
- Contact heat evoked potentials and quantitative thermal testing may provide useful information regarding patients with spinal cord injury and neuropathic pain.
- Alteration in the processing of somatosensory inputs from dermatomes rostral to the injury level in SCI patients with neuropathic pain (NP) may contribute to the understanding of the mechanisms underlying NP and secondary changes to neuropathic pain in SCI.

ABSTRACT

Objective: Neuropathic pain (NP) is a common symptom following spinal cord injury (SCI). NP may be associated with altered processing of somatosensory pathways in dermatomes rostral to the injury level. To explore this possibility, the characteristics of contact heat evoked potentials (CHEPs) and quantitative thermal testing (QTT) were studied at and above the lesion level in SCI patients with NP. The goal was to determine processing abnormalities correlated with data from clinical evaluations.
Methods: Thirty-two subjects with chronic NP, 22 subjects without NP and 16 healthy control subjects were studied. Warm and heat pain thresholds were determined both at and above SCI level. CHEPs were recorded above SCI level and subjects rated their perception of evoked heat pain using a numerical rating scale.
Results: CHEPs were not different between the three groups. Evoked pain perception in SCI subjects with NP was significantly higher than in SCI subjects without NP and healthy controls. Heat pain threshold was significantly lower in subjects with NP in comparison to both groups.
Conclusions: Our findings indicate that processing of somatosensory inputs from dermatomes rostral to the injury level is abnormal in SCI subjects with NP.
Significance: SCI somatosensory processing alteration may contribute to the understanding of the mechanisms underlying NP and secondary changes to NP in SCI.

1. Introduction

Around 50% of patients with spinal cord injury (SCI) suffer from neuropathic pain (NP) (Eide, 1998; Siddall et al., 2003; Finnerup et al., 2007; Soler et al., 2007). NP represents a major burden for SCI patients, however, the pathophysiological mechanisms mediating NP in SCI are currently poorly understood (Eide, 1998; Yezierski, 2005, 2009; Siddall et al., 2003; Finnerup et al., 2007; Wasner et al., 2008). When pain is perceived in regions without sensation below the SCI neurological level, NP is usually attributed, at least in part, to plastic changes in the central nervous system following deafferentation. Little is known about the central mechanisms involved in the initiation or maintenance of NP in SCI patients. However, there is evidence suggesting primary somatosensory cortex (S1) reorganization to an extent that correlates with pain intensity in limb amputees (Lotze et al., 2001) and in SCI patients (Wrigley et al., 2009).

* Corresponding author. Address: Institut Guttmann Hospital de Neurorehabilitació, Camí Can Ruti s/n. Barcelona, 08916 Barcelona, Spain. Tel.: +34 93 497 77 00; fax: +34 93 497 77 15.
E-mail address: hkumru@guttmann.com (H. Kumru).

1388-2457/$36.00
doi:10.1016/j.clinph.2011.07.038

The study of contact heat-evoked potentials (CHEPs) provides an objective evaluation method of small fibre function. The CHEP system delivers rapidly ramped heat stimuli that reliably evoke cortical potentials (Valeriani et al., 2002; Arendt-Nielsen and Chen, 2003). The CHEP system has been used for the study of various pain syndromes (Pralong et al., 2004; Atherton et al., 2007; Truini et al., 2007; Schestatsky et al., 2008). Evoked pain produced by thermal stimuli is a common characteristic of central pain (Vestergaard et al., 1995; Defrin et al., 2001; Finnerup et al., 2003). It has been suggested that an underlying neuronal hyperexcitability of the circuits mediating evoked pain might contribute to central NP (Cohen et al., 1996; Woolf and Salter, 2000; Finnerup et al., 2003; Finnerup and Jensen, 2004; Yezierski, 2005, 2009). In SCI patients with NP, the results of QTT in sites above the lesion level have given conflicting results: While some authors found reduced pain threshold for noxious electrical stimuli (Cohen et al., 1996), authors using QTT have reported either elevated threshold for heat pain (Defrin et al., 1999) and for cold and warm stimuli (Finnerup et al., 2003), or no changes at (Finnerup et al., 2007) and above the level of SCI (Wasner et al., 2008). Here, it was hypothesized that NP in SCI patients could be associated with altered processing of somatosensory pathways in dermatomes rostral to the injury level. The aim was to study the characteristics of CHEPs and of QTT in SCI subjects with and without NP at and above the lesion level and to determine to what extent these measures correlate with the clinical evaluation.

2. Materials and methods

Thirty-two subjects with SCI and NP (SCI-NP), 22 subjects with SCI without NP (SCI-noNP) and 16 healthy subjects were included in this study. The inclusion criteria for SCI-NP subjects were: (1) age over 18 years; (2) SCI at cervical (preserved sensory perception at C4 level (rostral limit of the lesion at C5 level, according to AIS (Marino et al., 2003)) or thoracic level; (3) complete or incomplete SCI (classified according to the American Spinal Injury Association "ASIA" Impairment Scale "AIS") (Marino et al., 2003); (4) chronic NP with more than 6 months duration, with pain intensity higher than 4 in a numerical rating scale (NRS); and (5) stable medical treatment for at least the last 3 weeks. The inclusion criteria for SCI-noNP subjects were the same except that they referred no pain (including spasm- and movement-related pain) at or below the neurological lesion level since the time of the injury, and they referred no acute pain episodes at least during the prior week. Healthy control subjects had to be free of any acute pain condition, medication and neurological disorders.

NP was diagnosed taking into account the localization and description of the pain. NP was defined as pain in an area of sensory abnormality corresponding to the spinal cord lesion. At injury level, subjects described pain as a burning, pressing, stabbing, or electrical quality sensation in the dermatomes at or just above the level of injury. Below-level NP was considered when burning, stabbing, or shooting pain was described as diffuse on regions at least two dermatomes below the SCI level. Pain did not have any primary relation to spasms or any other movement, had to have started after the SCI, be present for at least 6 months, and intensity of pain had to be higher than 4 on a numerical rating scale (NRS). Subjects with severe pain of other origin, such as musculoskeletal pain, were excluded.

Exclusion criteria were history of head trauma and history of any other chronic medical conditions (Bouhassira et al., 2004). The Institutional review board and the Ethical Committee of the institution revised and approved the protocol. All subjects or their representatives gave written informed consent.

2.1. Clinical evaluation of NP

All subjects underwent an interview before the neurophysiological evaluation to assess the clinical and phenomenological characteristics of pain: localization, descriptive characteristics, and intensity of NP. They were classified according to the ASIA Impairment Scale (AIS) categories: AIS-A, sensory-motor complete; AIS-B, motor complete, sensory incomplete; AIS-C, sensory-motor incomplete, with the average strength of the muscles below the level of lesion less than 3 (i.e., movement over the full range of motion against gravity) and AIS-D, sensory-motor incomplete, but with the average muscle strength equal to or above 3. In AIS-E subjects, a neurological impairment could no longer be present (Marino et al., 2003). The numerical rating scale (NRS), ranging from 0 for no pain to 10 for unbearable pain, was used for subjective assessment of the overall pain intensity perception and the score of ongoing pain (last 24 h). Patients completed the neuropathic pain symptom inventory (NPSI) for the assessment of NP characteristics (Bouhassira et al., 2004). All clinical evaluations and measurements of NP were performed by the same researcher (DS).

2.2. Contact heat evoked potentials (CHEPs)

Thermal stimuli were delivered using the Pathway device (Medoc, Ramat Yishai, Israel), equipped with a fast-heating/fast-cooling probe of 5.7-cm^2 surface area. Stimuli were delivered at the fastest available ramp rate of 70 °C/s from a baseline temperature of 32 °C to a maximum of 51 °C. A total of 14 stimuli were applied with an interstimulus interval of 30 s and to a slightly different spot in a square to reduce receptor fatigue or sensitization of skin overheating. CHEPs were obtained from all subjects at one dermatome (C4 sensory level, around the acromioclavicular joint). In subjects who reported more pain on one side, the stimulation was applied to that side. Subjects with NP who reported pain equally on both sides, subjects without NP and healthy controls were all stimulated on the dominant hand side.

CHEPs were recorded through a pair of 9 mm Ag/AgCl surface disc electrodes filled with conductive adhesive gel. The active electrode was placed on Cz and referenced to linked ears (A1–A2), where the pain related-evoked potentials are maximal (Bromm and Treede, 1984), with a ground placed on the right arm. The analysis time was 1 s. The amplifier band-pass frequency filter was 0.1–50 Hz. The gain was 50 μV/division. The impedance was kept less than 5 kOhm. CHEPs were recorded using routine electrodiagnostic equipment (Medelec Synergy, Oxford Instruments; Surrey, England).

2.3. Evoked pain perception

For each subject the NRS was recorded for their subjective evoked pain perception following each one of the 14 evoked potential recordings (see above).

2.4. Warm and heat pain threshold

Subjects were examined in the sitting position in a quiet room. Subjects were examined at two levels (above and at SCI) on both sides of the body (a total of four ASIA sensory points) (Marino et al., 2003). To evaluate a common point in each subject above the lesion, the C4 sensory level was used around the acromioclavicular joint (Marino et al., 2003) since all SCI subjects had lesions caudal to C4. Above the SCI level, the face was not stimulated because of brainstem innervations; C2 has a small innervated zone in the face and it does not allow for a convenient thermode placement, while in C3 some subjects had a scar after surgical intervention related to the accident. There was variation in the evaluated

sensory points between patients just at the level of lesion. Accordingly, in each healthy control, different sensory dermatomal points were used between C4–T12 for comparison of QTT at lesion level with SCI subjects.

Thermal threshold to warm sensation and heat pain were measured with a Medoc Thermal Sensory Analyser (Pathway; Medoc, Ramat Yishai, Israel) equipped with a 5.7 cm^2 probe, using the method of limits. Subjects were required to stop the progressive stimulus intensity increase by pressing a button as soon as they perceived the specific sensation being tested (4 stimuli for warm sensation and 4 stimuli for heat pain). In subjects with cervical lesions who were unable to use their hands, the button was placed under the wrist (this occurred just in one SCI-NP patient and in one SCI-noNP patient). The stimuli started at an adaptation temperature of 32 °C and increased at a rate of 1 °C/s. The cut-off temperature was 51 °C. Thresholds of warm and heat pain sensations were taken as the average of 4 successive readings in each session.

3. Experimental procedure

All SCI subjects and healthy controls underwent the following tests: (1) Clinical evaluation of NP; (2) psychophysical study of warm and heat pain threshold; (3) CHEPs; and (4) NRS for evoked pain perception during CHEPs. All three groups of subjects (SCI-NP, SCI-noNP and control subjects) were evaluated once.

All evaluations were performed in the morning while subjects were lying in a relaxed supine position in a warm and dimly lit room. Clinical evaluations of the subjects were performed by two investigators. The neurophsyiological and psychophysical evaluations were performed by a blinded investigator.

3.1. Data and statistical analysis

QTT was determined by calculating the mean threshold values for warm and heat pain. CHEPs, were averaged off-line with 14 individual traces collected from stimuli applied to the side where subjects reported more pain or dominant hand side in subjects with NP who reported pain equally on both side, subjects without NP and healthy controls. The mean latency of relevant peaks (N2 and P2) was measured as the time difference between the stimulus and each of the peaks, and the mean amplitude between the N2 and P2 peaks (N2/P2 amplitude). The mean and the SD were calculated for all variables. The data were collected from the painful side "PS" (where subjects reported more pain) (= dominant side) and non-painful or less painful side (= non-dominant side) in subjects with NP. If subjects with NP reported pain equally on both sides, the side with the dominant hand was used (= dominant side). This was also the case for healthy controls and subjects without NP. Handedness was determined according to the Edinburgh inventory (Oldfield, 1971).

For habituation rate, changes in evoked pain perception were calculated as the percentage of the NRS to the last stimulus with respect to the NRS to the first stimulus (habituation rate) for each subject during evoked potentials testing. Habituation rate in the amplitude of N2/P2 was calculated as the percentage of the amplitude of N2/P2 to the last stimulus with respect to the amplitude of N2/P2 to the first stimulus (habituation rate) for each subject.

The Kruskal–Wallis test and χ^2 tests were used for comparison of demographic and clinical data between groups of SCI subjects and healthy controls. Since the distribution of the data was not normal according to the Kolmogorov–Smirnov-test, the Kruskal–Wallis test was used for multiple comparisons between different groups, and Mann–Whitney *U* test for post hoc paired comparisons. Statistical analyses were performed using SPSS 13.0 software. Correlation analyses were done using the Spearman test for comparison of amplitude of CHEPs, demographic, clinical, and psychophysical characteristics. A value of $p \leqslant 0.05$ was considered for statistical significance.

4. Results

Clinical and demographic characteristics of all subjects are shown in Tables 1 and 2. There were no statistically significant differences between groups regarding age, gender, lesion level, and AIS grade ($p > 0.1$). Mean age was 48.8 ± 12.9 years for SCI-NP subjects; 45.7 ± 13.1 years for SCI-noNP subjects, and 44.0 ± 11.9 years for healthy controls (Kruskal–Wallis *H*; $p = 0.4$). The aetiology of the lesion in SCI subjects (with NP/ with noNP) was traumatic: 22/19; tumour: 1/1; myelitis: 3/2; vascular: 4/0; cervical myelopathy or disc herniation or related intervention: 2/0. The time since SCI was similar between subjects with and without NP (93.7 ± 118.2 months vs. 106.0 ± 98.3 months respectively; Mann–Whitney *U*: $p = 0.2$). There were no differences between subjects with and without NP in the lesion level and AIS grade. Twenty-one subjects with SCI-NP were taking gabapentin; 7 pregabalin; 18 benzodiazepine; 7 tramadol: 3 trazodona; 4 amitriptyline; 1 imipramine; 2 mirtazapine; 2 paroxetine; 1 clomipramine; 2 duloxetine; 2 venlafaxine; 6 baclofen.

4.1. Characteristics of patients with neuropathic pain

All subjects in the SCI-NP group had ongoing neuropathic pain at and/or below level (central pain) distributed in a diffuse or scattered manner for an average of 72.3 ± 89.9 months (range 7–438 months) (Table 1).

Pain was localized below-level only in 18 subjects, at-level only in 7 subjects and in both, at-level and below-level in another 7 subjects. In most subjects pain was bilaterally distributed. Only 2 subjects reported unilateral pain localization. The mean pain intensity was 7.9 (range 6–10) (Table 1). Fifty-six percentage of subjects reported pressing, 47% allodynia; 44% paroxysmal pain, 63% burning sensation; 22% dysestesia (Table 1).

4.2. Evoked potentials

There were no statistically significant differences in the N2 latency between subjects with NP (334.0 ± 73.3 ms), subjects without NP (302.5 ± 72.5 ms), and healthy controls (322.8 ± 95.2 ms). Results were similar for the P2 latency (414.0 ± 87.8 ms; 372.9 ± 80.7 ms, and 400.4 ± 105.5 ms, respectively in each of the three groups) (Kruskal–Wallis *H*; $p = 0.2$). Fig. 1 shows recordings of contact heat evoked potentials from three representative subjects.

N2/P2 amplitude was not different between subjects with NP, subjects without NP and healthy controls, as shown in Table 2 (Kruskal–Wallis *H*; $p = 0.3$). However habituation of evoked potential reduced significantly in subjects with NP in comparison to subjects without NP (Mann–Whitney *U*: $p < 0.0001$) and healthy controls ($p = 0.003$) (Table 2).

4.3. Psychophysical measures

Thresholds for warm and heat pain were similar between dominant and non-dominant side (PS or non-PS in SCI subjects with NP) for all groups ($p > 0.2$) (Figs. 2 and 3).

Above lesion level warm detection threshold was similar among the three groups ($p > 0.1$). However, at lesion level on both sides, warm detection threshold was significantly higher in subjects with NP and in subjects without NP than in healthy controls (Mann–Whitney *U*: $p \leqslant 0.01$ for each comparison, except non-dominant

Table 1
Clinical and demographical characteristic of SCI patients with NP and characteristic and subtype of neuropathic pain.

Age	Sex	Level of lesion	AIS	Level of pain	Localization of pain	NRS-ongoing pain	Pressing	Allodynia	Paroxysmal pain	Dysestesia	Burning
30	M	C4	C	Below	Abdomen	6	6	–	–	–	6
42	M	Th1	D	Below	Legs	8	–	–	9	–	8
35	M	C6	A	At	Arms	8	–	9	8	6	7
55	M	Th6	D	Below	Legs	9	7	7	–	6	–
44	F	C4	D	At	Arms	8	5	8	–	–	8
28	M	C7	B	Below	Legs, feet	7	7		–	–	–
64	M	Th3	D	Below	Legs, feet	8	–	6	8	–	–
68	F	C4	D	Below	Legs, feet	8	–	–	8	–	–
69	F	Th 10	A	Below	Legs, feet	8	–	–	8	8	8
40	M	Th 11	B	Below	Legs, feet	8	–	–	8	–	8
61	M	Th3	D	At	Thorax	7	9	–	–	–	7
40	M	C5	B	At	Arms	8	–	–	–	–	8
46	M	Th4	A	At	Thorax	8	8	–	–	–	8
61	M	Th3	B	Below	Legs	8	8	–	–	–	–
50	M	C4	D	Below	Abdomen	6	8	8	–	–	–
57	F	Th9	D	At–below	Abdomen, legs	7	7	–	10	–	7
53	F	Th2	D	Below	Genital area	8	7	8	–	–	8
60	F	Th4	A	At–below	Thorax, genital area	9	5	10	9	–	–
47	F	Th12	D	Below	Legs, feet	10	10	–	–	–	10
62	M	Th11	A	Below	Legs	9	9	9	10	–	–
61	M	Th12	A	Below	Genital area	10	10	10	–	–	–
42	M	Th5	A	Below	Genital area, feet	8	8	–	–	–	–
66	M	Th12	D	Below	Legs	8	–	6	8	5	–
33	M	C7	A	Below	Legs	7	–	7	–	–	8
34	M	Th6	C	At	Abdomen	7	–	10	–	–	10
53	F	Th7	D	At	Abdomen	8	–	3	10	–	10
29	F	Th8	D	At–below	Abdomen, legs, feet	9	–	10	–	9	4
36	F	Th8	C	At–below	Adbomen–feet	8	7	9	6	9	9
60	M	Th6	D	Below	Legs, feet	8	–	–	–	7	4
57	M	C5	D	At–below	Arms, feet	9	9	–	7	–	10
27	M	C6	A	At–below	All body (below SCI)	7	7	–	–	–	7
50	M	Th12	A	At–below	Legs, feet	8	–	–	10	–	–

M: male; F: female; C: cervical; Th: thoracic; AIS: ASIA Impairment Scale (grade A, B, C, D).

Table 2
Numerical rating scale for ongoing pain and for evoked pain perception, habituation rate for last stimulus, contact heat evoked potentials (CHEPs).

Subjects	NRS-ongoing pain	NRS-evoked pain	Habituation rate in evoked pain (%)	Amplitude of N2-P2 (μV)	Habituation rate in amplitude of N2-P2 (%)
SCI with NP	7.9 (1.0)	4.6 (2.1)	102.3 (70.9)	42.3 (23.0)	94.9 (51.8)
SCI without NP	–	3.1 (1.2)*	63.1 (66.8)*	37.8 (23.8)	39.3 (48.9)*
Healthy controls	–	2.4 (1.1)*	46.0 (40.9)*	34.7 (19.2)	46.6 (41.0)*

SCI: spinal cord injury; NP: neuropathic pain; NRS: Numerical rating scale. The numbers in brackets are standard deviation (SD).
* $p < 0.05$ (Mann–Whitney U) between patients with neuropathic pain (NP) and patients without NP; patients with NP and healthy controls.

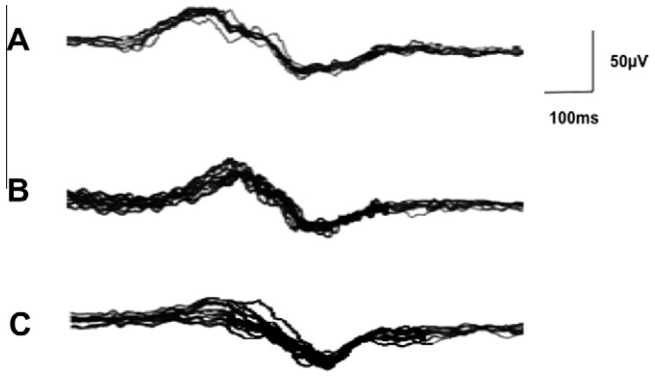

Fig. 1. Recordings of contact heat evoked potentials from three representative subjects. (A) a patient with incomplete SCI-NP (AIS-D) at C4 level; (B) a patient with incomplete SCI-noNP at C5 level (AIS-D); and (C) a healthy control. Fourteen traces are superimposed in each graph. The whole recording time was 1000 ms.

side of subjects without NP vs. healthy controls "$p = 0.06$"), but it was not different between subjects with NP vs. subjects without NP ($p > 0.1$) (Fig. 2).

The heat pain threshold above and at lesion level was significantly lower in subjects with NP in comparison to SCI subjects without NP and healthy controls (Mann–Whitney U: $p < 0.04$), but it was not different between SCI subjects with NP and healthy controls (Fig. 3).

Evoked heat pain perception measured on the dominant side at C4 level was significantly higher in SCI subjects with NP in comparison to SCI subjects without NP or healthy controls (Mann–Whitney U: $p < 0.005$ for each comparison), but it was not different between SCI subjects without NP and healthy controls (Mann–Whitney U: $p = 0.3$).

Habituation of subjective evoked heat pain perception, measured by NRS, was significantly less in subjects with NP in comparison to subjects without NP (Mann–Whitney U: $p = 0.046$) and healthy controls ($p = 0.002$) (Table 2).

There was no correlation between ongoing pain score, evoked pain perception and CHEPs amplitude in subjects with NP ($p > 0.07$).

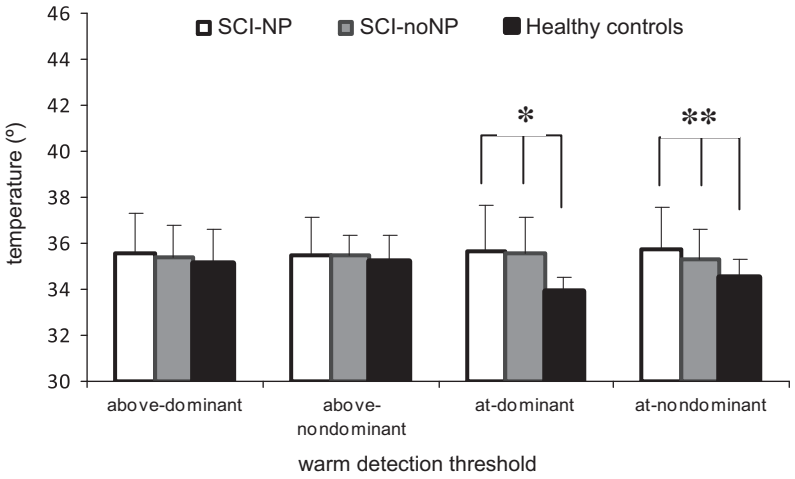

Fig. 2. The average of warm detection threshold (± standard deviation) in patients with spinal cord injury and with neuropathic pain (SCI-NP) and in patients with SCI-noNP and in healthy controls. Dominant side (or Painful side), non-dominant side (or non-painful or less painful side) above or at SCI. $^{*}p < 0.05$ between healthy controls vs. Bold values indicates significant p values ($p \leqslant 0.05$). $^{**}p < 0.05$ between healthy controls vs. SCI-NP patients, and vs. just dominant hand side in SCI-noNP patients ($p = 0.06$ between healthy controls and non-dominant hand side of patient with noNP).

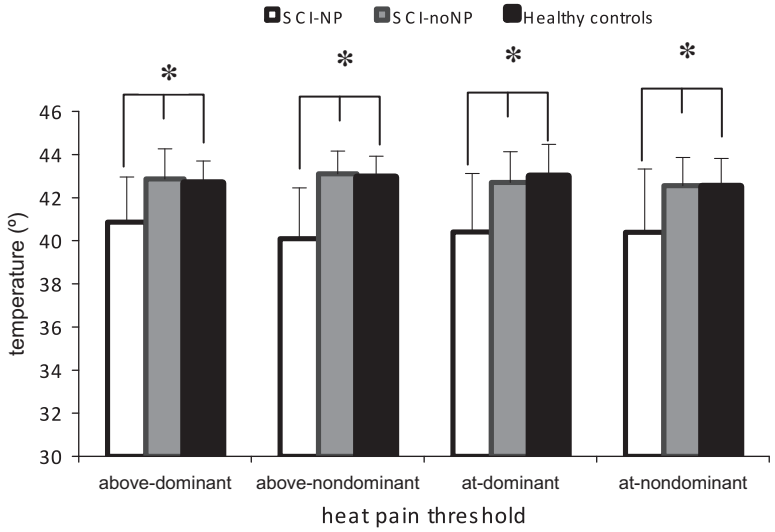

Fig. 3. The average of heat pain perception in patients with spinal cord injury and with neuropathic pain (SCI-NP) and in patients with SCI-noNP and in healthy controls. Dominant side (where patient reported more pain; or dominant hand side in patient with NP, who reported pain equally on both side, and in patients without NP and healthy controls). Non-dominant side (non-painful or less painful side in patients with NP or non-dominant hand side in patients noNP and in healthy controls) above or at SCI. $^{*}p < 0.05$ between patients with SCI-NP and patients with SCI-noNP; between patients with SCI-NP and healthy controls.

Table 3
NRS-ongoing pain and for evoked pain, amplitude of contact heat evoked potential, warm and heat pain threshold at different AIS sensory points at and above the lesion level in complete vs. incomplete SCI; in cervical vs. thoracic SCI. SCI-NP patients, and vs. SCI-noNP patients.

	Level	Side	Complete SCI	Incomplete SCI	p	Cervical sci	Thoracic SCI	p
Ongoing pain			8.2 (0.2)	7.9 (0.9)	0.35	7.4 (1.0)	8.2 (0.8)	**0.02**
Evoked pain	C4	Dominant	4.3 (1.4)	4.7 (2.4)	0.51	5.7 (2.1)	4.1 (1.9)	0.07
Amplitude of N2/P2	C4	Dominant	37.0 (19.9)	44.7 (24.4)	0.36	55.7 (17.2)	36.4 (23.6)	**0.01**
Warm perception threshold	At	Dominant	35.5 (2.2)	35.7 (1.9)	0.81	36.4 (2.5)	35.3 (1.7)	0.23
	At	Non-dominant	36.1 (2.4)	35.5 (1.6)	0.53	36.1 (2.2)	35.5 (1.7)	0.51
	Above	Dominant	35.9 (2.5)	35.7 (1.7)	0.82	35.1 (0.7)	36.0 (2.3)	0.09
	Above	Non-dominant	35.9 (1.3)	35.3 (1.3)	0.26	35.0 (1.1)	35.7 (1.7)	0.18
Heat pain threshold	At	Dominant	39.9 (2.8)	40.7 (2.7)	0.50	41.2 (2.5)	40.0 (2.8)	0.25
	At	Non-dominant	40.1 (2.7)	40.6 (3.1)	0.66	40.6 (3.4)	40.0 (3.0)	0.66
	Above	Dominant	40.9 (2.3)	40.9 (2.0)	0.99	40.4 (2.3)	41.1 (2.0)	0.41
	Above	Non-dominant	39.9 (2.5)	40.2 (2.3)	0.68	39.6 (2.8)	40.3 (2.2)	0.45

Dominant side (or painful side in SCI-NP, and dominant hand side in SCI-without NP and healthy subjects), non-dominant side (or non-painful or less painful side or non-dominant hand side) above or at SCI.
C4: at the cervical dermatome 4; AIS: ASIA Impairment Scale (grade A, B, C, D).

4.4. Complete vs. incomplete spinal cord injury

No significant differences were found in CHEPs or evoked pain perception, nor in warm or in heat pain threshold at or above the injury level between complete SCI subjects and incomplete SCI subject ($p > 0.1$) (Table 3).

No correlation was found between the amplitude of CHEPs, ongoing pain and evoked pain perception in complete or incomplete SCI and NP ($p > 0.2$).

4.5. Cervical vs. thoracic spinal cord injury

The amplitude of evoked potentials was significantly higher in subjects with cervical SCI than in those with thoracic SCI subjects ($p = 0.01$). Ongoing pain was significantly lower in cervical SCI subjects than in thoracic SCI subjects ($p = 0.02$) (Table 3). There were no significant differences in evoked heat pain perception, neither in warm and heat pain threshold between SCI-NP subjects with thoracic vs. with cervical SCI ($p > 0.06$) (Table 3).

There was no correlation between the amplitude of CHEPs, ongoing pain and evoked heat pain perception in cervical or thoracic SCI subjects ($p > 0.1$).

5. Discussion

This study found: (1) reduced heat pain thresholds, (2) reduced habituation in the amplitude of evoked potentials and evoked heat pain and (3) increased ratings to evoked heat pain in dermatomes rostral to the injury level in subjects with SCI-NP, which are pointing toward central sensitization. In addition, the amplitude of CHEPs was significantly larger in subjects with cervical SCI in comparison to those with thoracic SCI.

5.1. Evoked potentials (N2/P2 amplitude)

The CHEPs amplitude recorded above the lesion level was not different in SCI-NP subjects in comparison to SCI-noNP subjects or control subjects.

In control subjects, the amplitude of Laser evoked potentials (LEPs) recorded at the vertex correlates positively with the subjective sensation of pain (Treede, 1995; Treede et al., 2003). In subjects with neuropathic pain, be more related to sensory deficits than to evoked pain sensations (García-Larrea et al., 1997; Garcia-Larrea et al., 2002; Hatem et al., 2010). LEPs were attenuated significantly after stimulation over the painful territory in subjects with central pain, including those with hyperalgesic reactions to laser (Cohen et al., 1996) or to heat pain (Schestatsky et al., 2008), which likely reflects deafferentation in spino-thalamo-cortical path. In this study, CHEPs were recorded on the dermatome rostral to the spinal cord injury (intact area) and where subjects did not present any neurological deficit and/or neuropathic pain. This might explain why no differences in the amplitude of evoked potentials in subjects with NP in comparison to patients without NP and healthy controls were found.

The higher amplitude of CHEPs in cervical SCI might be a sign of "greater central reorganization" following extended deafferentation.

5.2. Psychophysical measures

Subjects with SCI-NP and with SCI-noNP subjects had higher warm detection thresholds at lesion level, but not above. This finding is compatible with the findings of Nicotra and Ellaway (2006), who reported subclinical thermal sensory deficit in dermatomes just above the lesion, clinically defined as normal, in complete and incomplete SCI. Those authors (Nicotra and Ellaway, 2006) found normal warm detection thresholds one to two dermatomes immediately above the lesion level. Therefore, it could be that warm threshold abnormalities could be found in dermatomes clinically defined as normal in some subjects with cSCI or iSCI, but may not be a generalized finding (Nicotra and Ellaway, 2006; Savic et al., 2007).

Lower heat pain thresholds have been reported for noxious electrical stimuli delivered at and above the level of complete or incomplete SCI subjects with chronic pain when compared to healthy adults (Cohen et al., 1996). Defrin et al. (1999), found an elevation in heat pain threshold above the level of injury in SCI subjects with pain and functionally complete spinal transection. However no changes in heat pain threshold were reported by Wasner et al. (2008), above level (in the face) or by Finnerup et al. (2007), and by Savic et al. (2007), at SCI level. The different result in psychophysical measures between those studies might be due to the selection of subjects, pain characteristic, and methodological differences which were used in each study.

Reduced heat pain threshold, increased ratings to evoked heat pain and reduced habituation in the amplitude of evoked potentials and of evoked heat pain in dermatomes rostral to the injury level in SCI-NP subjects suggests an increased excitability of the nociceptive pathways out of the pain areas. The mechanisms responsible for NP in SCI may include among others: interrupted sensory pathways, interference with inhibitory pathways and modulation of cell assemblies engaged in sensory inhibition (Melzack and Loeser, 1978; Woolf et al., 1998; Eide, 1998; Yezierski, 2005, 2009; Wrigley et al., 2009). Interruption of ascending spinal pathways disrupts thalamic function, resulting in loss of inhibitory effects of the afferent impulses. Melzack and Loeser (1978) proposed that such a massive deafferentation produces a burst of abnormal activity in dorsal horn cells and thalamus that can last for months following cessation of stimulation. The massive deafferentation following SCI could lead to neuronal hyperexcitability and finally to pain (Eide et al., 1996; Eide, 1998). Such a generalized sensitization has been reported previously in SCI (Cohen et al., 1996).

Chronic NP may induce secondary changes in the central nervous system, such as increased response to painful stimuli (hyperalgesia) (Woolf and Salter, 2000; Jensen et al., 2001). There may be changes in the pain suppression systems. One example is the diffuse noxious inhibitory control (DNIC), (Dickenson et al., 1980) in which distant noxious inputs activate a spinal–brainstem–spinal feedback loop, which subsequently inhibits pain (Roby-Brami et al., 1987). Here we can hypothesize that, in SCI-NP subjects, the DNIC system may not work properly, whereas central sensitization in turn could be the cause of the changes in pain perception threshold and evoked pain perception, which are not dependent on distance from the SCI.

5.3. Habituation of evoked potentials and evoked heat pain perception

Habituation is a physiological phenomenon of the sensory cortex that progressively reduces its activity to repetitive stimuli. An evoked response may develop habituation to a lesser degree if the brain areas that generate it are more excitable, or because the central nervous system structures that regulate habituation are less active, e.g., hypoexcitable (Becerra et al., 1999; Valeriani et al., 2003; de Tommaso et al., 2005a,b; Greffrath et al., 2007). Reduced habituation of nociceptive evoked potentials has been reported in patients with migraine, which probably reflects an abnormal excitability of the cortical areas involved in pain processing (Valeriani et al., 2003; de Tommaso et al., 2005b). The subjects in this study with SCI-NP showed significantly less habituation,

which can suggest more excitable brain areas, and/or less active centers regulating habituation.

6. Conclusion

The findings of this study indicate that NP in SCI subjects is associated with altered processing of somatosensory pathways in dermatomes rostral to the injury level. Although the pathophysiology of ongoing NP is different from that of thermal hyperalgesia and of evoked pain in dermatomes rostral to the injury level, we consider that our results may contribute to the understanding of the mechanisms underlying NP and of subsequent changes to neuropathic pain.

Acknowledgements

This work was supported in part by grant PI082004 and PI10/00442 from the Instituto de Salud Carlos III, grants from a BBVA Translational Research Chair in Biomedicine, and the Foundation La Marató TV3 with grants number 071930 and 071931.

References

Arendt-Nielsen L, Chen AC. Lasers and other thermal stimulators for activation of skin nociceptors in humans. Neurophysiol Clin 2003;33:259–68.
Atherton DD, Facer P, Roberts KM, Misra VP, Chizh BA, Bountra C. Use of the novel contact heat evoked potential stimulator (CHEPS) for the assessment of small fibre neuropathy: correlations with skin flare responses and intra-epidermal nerve fibre counts. BMC Neurol 2007;7:21.
Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, et al. Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. Magn Reson Med 1999;41:1044–57.
Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–57.
Bromm B, Treede RD. Nerve fibre discharges, cerebral potentials and sensations induced by CO_2 laser stimulation. Hum Neurobiol 1984;3(1):33–40.
Cohen MJ, Song ZK, Schandler SL, Ho WH, Vulpe M. Sensory detection and pain threshold in spinal cord injury patients with and without dysesthetic pain and in chronic low back pain patients. Somatosens Mot Res 1996;13:29–37.
Defrin R, Ohry A, Blumen N, Urca G. Acute pain threshold in subjects with chronic pain following spinal cord injury. Pain 1999;83:275–82.
Defrin R, Ohry A, Blumen A, Urca G. Characterization of chronic pain and somatosensory function in spinal cord injury subjects. Pain 2001;89:253–63.
de Tommaso M, Losito L, Libro G, Guido M, Di Fruscolo O, Sardaro M, et al. Effects of symptomatic treatments on cutaneous hyperalgesia and laser evoked potentials during migraine attack. Cephalalgia 2005a;25:359–68.
de Tommaso M, Lo Sito L, Di Fruscolo O, Sardaro M, Pia Prudenzano M, Lamberti P, et al. Lack of habituation of nociceptive evoked responses and pain sensitivity during migraine attack. Clin Neurophysiol 2005b;116:1254–64.
Dickenson AH, Le Bars D, Besson JM. Diffuse noxious inhibitory controls (DNIC). Effects on trigeminal nucleus caudalis neurones in the rat. Brain Res 1980;200:293–305.
Eide PK, Jørum E, Stenehjem AE. Somatosensory findings in patients with spinal cord injury and central dysaesthesia pain. J Neurol Neurosurg Psychiatry 1996;60:411–5.
Eide PK. Pathophysiological mechanisms of central neuropathic pain after spinal cord injury. Spinal Cord 1998;36:601–12.
Finnerup NB, Johannesen IL, Bach FW, Jensen TS. Sensory function above lesion level in spinal cord injury patients with and without pain. Somatosens Mot Res 2003;20:71–6.
Finnerup NB, Jensen TS. Spinal cord injury pain-mechanisms and treatment. Eur J Neurol 2004;11:73–82 [Review].
Finnerup NB, Sørensen L, Biering-Sørensen F, Johannesen IL, Jensen TS. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. Exp Neurol 2007:139–49.
García-Larrea L, Peyron R, Laurent B, Mauguière F. Association and dissociation between laser-evoked potentials and pain perception. Neuroreport 1997;8(17):3785–9.
Garcia-Larrea L, Convers P, Magnin M, André-Obadia N, Peyron R, Laurent B, et al. Laser evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. Brain 2002;125:2766–81.
Greffrath W, Baumgärtner U, Treede RD. Peripheral and central components of habituation of heat pain perception and evoked potentials in humans. Pain 2007;132(3):301–11.
Hatem SM, Attal N, Ducreux D, Gautron M, Parker F, Plaghki L, et al. Clinical, functional and structural determinants of central pain in syringomyelia. Brain 2010;133:3409–22.
Jensen TS, Gottrup H, Sindrup SH, Bach FW. The clinical picture of neuropathic pain. Eur J Pharmacol 2001;429:1–11.
Lotze M, Flor H, Grodd W, Larbig W, Birbaumer N. Phantom movements and pain. An fMRI study in upper limb amputees. Brain 2001;124:2268–77.
Marino RJ, Barros T, Biering-Sorensen F, Burns SP, Donovan WH, Graves DE, et al. 2002 ANSC. International standards for neurological classification of spinal cord injury. J Spinal Cord Med 2003;26:S50–6.
Melzack R, Loeser JD. Phantom body pain in paraplegics: evidence for a central "pattern generating mechanism" for pain. Pain 1978;4:195–210.
Nicotra A, Ellaway PH. Thermal perception thresholds: assessing the level of human spinal cord injury. Spinal Cord 2006;44:617–24.
Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
Pralong E, Pollo C, Bloch J, Villemure JG, Daniel RT, Tétreault MH, et al. Recording of ventral posterior lateral thalamus neuron response to contact heat evoked potential in patient with neurogenic pain. Neurosci Lett 2004;367:332–5.
Roby-Brami A, Bussel B, Willer JC, Le Bars D. An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Probable involvement of a supraspinal loop. Brain 1987;110:1497–508.
Savic G, Bergström EM, Davey NJ, Ellaway PH, Frankel HL, Jamous A, et al. Quantitative sensory tests (perceptual thresholds) in patients with spinal cord injury. J Rehabil Res Dev 2007;44:77–82.
Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 2003;103:249–57.
Schestatsky P, Lladó-Carbó E, Casanova-Molla J, Alvarez-Blanco S, Valls-Solé J. Small fibre function in patients with meralgia paresthetica. Pain 2008;139:342–8.
Soler MD, Sauri-Ruiz J, Curcoll ML, Benito-Penalva J, Opiso-Salleras E, Vidal-Samsó J. Characteristics of chronic neuropathic pain and their relationship with psychological well-being in spinal cord injury patients. Rev Neurol 2007;44:3–9.
Treede RD. Peripheral acute pain mechanisms. Ann Med 1995;27:213–6 [Review].
Treede RD, Lorenz J, Baumgartner U. Clinical usefulness of laser-evoked potentials. Neurophysiol Clin 2003;33:303–14.
Truini A, Galeotti F, Pennisi E, Casa F, Biasiotta A, Cruccu G. Trigeminal small fibre function assessed with contact heat evoked potentials in humans. Pain 2007;132:102–7.
Valeriani M, Le Pera D, Niddam D, Chen AC, Arendt-Nielsen L. Dipolar modelling of the scalp evoked potentials to painful contact heat stimulation of the human skin. Neurosci Lett 2002;318:44–8.
Valeriani M, de Tommaso M, Restuccia D, Le Pera D, Guido M, Iannetti GD, et al. Reduced habituation to experimental pain in migraine patients: a CO(2) laser evoked potential study. Pain 2003;105:57–64.
Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. Pain 1995;61:177–86.
Wasner G, Lee BB, Engel S, McLachlan E. Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. Brain 2008;131:2387–400.
Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, et al. Towards a mechanism-based classification of pain? Pain 1998;77:227–9.
Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765–9.
Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, Middleton JW, Henderson LA, Siddall PJ. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain 2009;141:52–9.
Yezierski RP. Spinal cord injury: a model of central neuropathic pain. Neurosignals 2005;14:182–93.
Yezierski RP. Spinal cord injury pain: spinal and supraspinal mechanisms. J Rehabil Res Dev 2009;46:95–108.