Residual spinothalamic tract pathways predict development of central pain after spinal cord injury

Gunnar Wasner,¹,² Bonsan Bonne Lee,²,⁴ Stella Engel²,⁴ and Elspeth McLachlan¹,²

¹Prince of Wales Medical Research Institute, ²University of New South Wales, Australia, ³Department of Neurology, Division of Neurological Pain Research and Therapy, University-Clinic of Schleswig-Holstein, Campus Kiel, Germany and ⁴Prince of Wales Hospital, Randwick, Sydney, NSW, Australia

Correspondence to: Priv.-Doz. Dr Med. Gunnar Wasner, Department of Neurology, Division of Neurological Pain Research and Therapy, University Hospital of Schleswig-Holstein, Campus Kiel, Schittenhelmstrasse 10, 24105 Kiel, Germany
E-mail: g.wasner@neurologie.uni-kiel.de

Central neuropathic pain following lesions within the CNS, such as spinal cord injury, is one of the most excruciating types of chronic pain and one of the most difficult to treat. The role of spinothalamic pathways in this type of pain is not clear. Previous studies suggested that spinothalamic tract lesions are necessary but not sufficient for development of central pain, since deficits of spinothalamic function were equally severe in spinal cord injured people with and without pain. The aim of the present study was to examine spinothalamic tract function by quantitative sensory testing before and after activation and sensitization of small diameter afferents by applying menthol, histamine or capsaicin to the distal skin areas where spontaneous pain was localized. Investigations were performed in matched groups each of 12 patients with and without central pain below the level of a clinically complete spinal cord injury, and in 12 able-bodied controls. To test peripheral C fibre function, axon reflex vasodilations induced by histamine and capsaicin applications were quantified. In eight patients with pain, sensations of the same quality as one of their major individual pain sensations were rekindled by heat stimuli in combination with topical capsaicin (n = 7) or by cold stimuli (n = 1). No sensations were evoked in pain-free patients (P < 0.01). Capsaicin-induced axon reflex vasodilations were significantly larger in pain patients with heat- and capsaicin-evoked sensations in comparison to pain patients without capsaicin-provoked sensations. These results suggest that intact thermosensitive nociceptive afferents within lesioned spinothalamic tract pathways distinguish people with central pain from those without. The ability to mimic chronic pain sensations by activation of thermosensory nociceptive neurons implies that ongoing activity in these residual spinothalamic pathways plays a crucial role in maintaining central pain. We propose that processes associated with degeneration of neighbouring axons within the tract, such as inflammation, may trigger spontaneous activity in residual intact neurons that act as a ‘central pain generator’ after spinal cord injury.

Keywords: spinal cord injury; central neuropathic pain; spinothalamic tract; sensitization; nociceptive afferents

Abbreviations: NRS = numeric rating scales; SCI = spinal cord injury; ZPP = zone of partial preservation


Introduction

Central pain that develops after lesions within the CNS, such as stroke, spinal cord injury (SCI) and multiple sclerosis, is one of the most excruciating and therapeutically refractory types of neuropathic pain (Finnerup et al., 2005; Siddall and Middleton, 2006). One reason for the lack of success in treating these types of pain is that the mechanisms underlying central pain are not fully understood.

A particularly puzzling question has been the role of the spinothalamic tract in central pain syndromes (Finnerup and Jensen, 2004). Multiple studies in central pain patients performed over the last two decades have demonstrated deficits of temperature and pain sensation within the painful area indicating that lesions of the spinothalamic projections are essential for development of pain (Beric et al., 1988; Boivie et al., 1989; Parent et al., 1992; Vestergaard et al., 1995; Eide et al., 1996; Bowsher et al., 1998; Defrin et al., 2001; Finnerup et al., 2003; Finnerup and Jensen, 2004; Österberg et al., 2005; Ducruex et al., 2006; Finnerup et al., 2007a). However, as differences in altered sensitivity to thermal and nociceptive stimuli were not found in patients with pain compared to patients without pain after central lesions,
it has been suggested that such lesions alone are not sufficient to generate central pain (Defrin et al., 2001; Finnerup et al., 2003; Finnerup and Jensen, 2004; Ducoux et al., 2006; Siddall and Middleton, 2006; Finnerup et al., 2007a). Thus, despite clear evidence for their relevance, the exact impact of lesions of the spinothalamic tract remains unclear.

About 30–40% of spinal cord injured people suffer from neuropathic pain due to lesions of nervous structures after SCI (Störm et al., 1997; Siddall et al., 1999, 2003). In the taxonomy of the International Association for the Study of Pain (IASP), at-level pain, i.e. neuropathic pain related to the level of the injury, is distinguished from below-level pain localized distal from the site of injury (Siddall et al., 2000, 2002, 2003; Vierck et al., 2000). While at-level pain may be driven by both peripheral and central components, below-level pain is considered to be a central pain syndrome directly caused by the lesion to the spinal cord (Siddall et al., 2000; Finnerup and Jensen, 2004; Wasner et al., 2007). In terms of the underlying pathophysiology, it has been proposed that, after SCI, abnormal activity may arise as a result of a ‘spinal pain generator’ formed by neuronal hyperexcitability at the lesion site due to release of the excitatory amino acid glutamate, up-regulation of sodium channels, activation of glial cells during inflammatory processes triggered by the lesion and loss of intraspinal and descending inhibitory pathways (Vierck et al., 2000; Finnerup and Jensen, 2004; Yezierski, 2005; Waxman and Hains, 2006). This is in accord with a recent patient study indicating that neuronal hyperexcitability in the spinal cord is a key element in central neuropathic pain, whereas loss of spinothalamic function does not appear to be a pain predictor (Finnerup et al., 2007b). As preserved neuronal function is essential for development of hyperexcitability, the question arises as to whether residual intact spinothalamic tract neurons can be identified in subjects with central pain following SCI.

In the present study, spinothalamic tract function was tested quantitatively in people with and without below-level pain following clinically complete SCI by quantitative sensory testing before and after activation and sensitization of small diameter afferents by applying menthol, histamine or capsaicin to the distal skin areas where spontaneous pain was localized. The responses to these three chemicals can be used to activate specific spinothalamic tract pathways. We reasoned that stimulation after sensitization of small fibre peripheral afferents including nociceptors and thermal afferents in a below-level area with severe sensory deficits might generate sensations that were missed by conventional quantitative sensory testing (Wasner et al., 2007). This would imply the existence of persisting connections between the periphery and the central pathways.

**Materials and Methods**

**Subjects**

The function of the spinothalamic tract was tested in three groups each of 12 age- and sex-matched subjects: (i) SCI people without any pain below the lesion and (ii) SCI people with central neuropathic pain below the spinal lesion, (iii) able-bodied pain-free control subjects (Tables 1–3).

SCI subjects were included according to the following criteria. To ensure a central lesion affecting the spinal cord above the conus medullaris, we required (i) that the traumatic SCI was not lower than the 10th thoracic vertebra and (ii) at least one clinical sign at or proximal to the neurological level of the test area indicated a central lesion (e.g., brisk Achilles jerks when testing the lower leg). Patients had to be classified as having a complete spinal cord lesion according to the American Spinal Injury Association’s standards for classification of SCI (ASIA, grade A, see later). In cases in which patients had a zone of partial preservation (ZPP, see later), this needed to be well localized outside the test area.

Neuropathic pain was defined as chronic pain in an area of sensory abnormalities developed after SCI. The definition of below-level pain was that the painful area was at least two dermatome segments below the lesion level to ensure that the pain was localized below the neurological level (Finnerup et al., 2003) (Table 1). The pain needed not to have any primary relation to spasm or any other movement.

SCI pain-free control subjects should not have had any sensation and particularly not pain (including any spasm- or movement-related pain) below the neurological level since the time of the injury (Table 2).

Able-bodied control subjects had to be free of any chronic or acute pain, any medication and any neurological disorder.

Subjects with a mental disease that potentially interfered with their ability to be tested psychophysically, those with evidence of any other disease affecting the central or the peripheral nervous system, those with evidence of allergies to menthol, histamine or capsaicin, those younger than 18 years old and those who were pregnant were excluded from the study.

All experiments were performed in the supine position in a room held at a temperature of 22–23°C and a relative humidity of 50–60%.

The study was approved by the local human research ethics committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. All participants gave informed written consent to participate in the study.

**Medical history and pain characteristics**

Medical histories were obtained (Tables 1–3). Patients localized their neurological level and pain on a body chart in two dimensions (anterior and posterior) (Finnerup et al., 2003). SCI patients with below-level pain were asked to characterize the quality of their below-level pain by a maximum of three descriptors chosen from a modified short-form McGill Pain Questionnaire or by using their own words when the pain quality was not represented by any of the given descriptors. The Questionnaire contained the following items: throbbing, shooting, stabbing, sharp, cramping, gnawing, burning, hot, cold, aching, heavy, tender, dull, touch-evoked, tingling, wrenching (Wasner et al., 2002). Furthermore, the patients rated their average pain intensity and the average intensity of any temperature component accompanying the pain on numeric rating scales (pain rating: NRS 0–10, 0 = no pain, 10 = maximum conceivable pain; temperature rating: NRS –10 to +10, –10 = maximum
conceivable sensation of cold, 0 = neutral temperature sensation, +10 = maximum conceivable sensation of heat).

**Clinical examination**
A complete neurological and physical examination was performed. Spinal lesions were classified according to the American Spinal Injury Association’s (ASIA) standards (Maynard *et al*., 1997). In addition to the required testing for touch and pinprick to estimate sensory function according to the ASIA standard, vibration was tested with a graded tuning fork (64 Hz, 8/8 scale) that was placed over a bony prominence close to the test area in the lower extremity and left there until the subject could no longer feel vibration. Vibration detection threshold was determined as a disappearance threshold (Whitten *et al*., 2005).

Spasticity was assessed by using the spasm frequency scale [ranging from 0 (no spasm) to 4 (>10 spasm per day)] (Snow *et al*., 1990) and the modified Ashworth Scale [ranging from 0 (no increase in tone) to 4 (two people required to abduct the hips to 45°)] (Bohannon and Smith, 1987).

**Quantitative sensory testing**
Quantitative mechano- and thermosensory testing was conducted in all subjects. Initially, all sensory tests to be used were demonstrated in an area of unaffected skin (e.g. the arm in SCI people with thoracic lesions and healthy controls or the neck in people with cervical lesions) to make the subjects familiar with the applied stimuli. After these trials were complete, measurements were first made in the face of all subjects. The face served as an unaffected control area well above the neurological level primary affected by the SCI. Next, these tests were performed before and after chemical sensitization of small fibre afferents in the area of below-level pain in the subjects with pain and topographically corresponding areas in pain-free SCI people and healthy controls.

To distinguish any stimulus-evoked sensation in the area below the neurological level from ongoing sensations or any imagined sensation, the stimulus was applied when the subject had their eyes closed and the site of stimulation identified afterwards.

In cases of severe sensory loss, failure to respond to cut-off-limits of the test apparatus resulted in assignment of the cut-off limits as the threshold value.

Figure 1 gives an overview over the experimental protocol.

**Quantitative mechano-sensory testing**
Mechanical detection and pain thresholds to punctuate stimuli were measured using a set of 12 von Frey hairs with a bending force ranging from 0.25 to 512 mN (Optihair2-Set, Marstock Nervtest, Germany). Using the method of limits, two determinations for detection and pain thresholds were made, each with a series of ascending and descending stimulus intensities. Thresholds were indicated verbally by the subjects. Stimulus-evoked pain was rated on a numerical rating scale (NRS 0–10, see above). The final thresholds and pain ratings at threshold were the geometric mean of these two series (Rolke *et al*., 2006).

Mechanical dynamic allodynia was investigated by gently moving a cotton swab over the skin three times at a frequency of 0.2 Hz. The subjects rated the pain intensity by giving one average NRS value (0–10) for these three stimuli.

When punctuate hyperalgesia was indicated by a decreased pain threshold to punctuate stimuli or by the presence of mechanical dynamic alldynia, the corresponding areas of mechanically evoked pain were determined by marking the border between areas of non-painful and painful stimulation (Wasner *et al*., 2004).

**Quantitative thermotesting**
Quantitative thermotesting was performed with a thermostest device (TSA 2001-II, Medoc, Israel) to investigate perception thresholds for warmth, cold, heat pain and cold pain (Fruhstorfer *et al*., 1976; Yarnitsky and Ochon, 1991). According to the standards of the German Research Network on Neuropathic Pain, the method of limits was used by applying ramp stimuli at a velocity of 1°C/s starting from 32°C applied to the skin via a Peltier type thermode (3 × 3 cm²) (Rolke *et al*., 2006). The subjects were asked to press a button when the respective thermal sensation was perceived. In case of inability to press the button due to SCI-related paresis, sensations were reported verbally to the investigator who pressed the button immediately. Cut-off temperatures were 0 and 50°C.

**Thermally induced sensations**
During investigations of thermal pain thresholds, the subjects were instructed to rate the perceived pain and temperature sensations at the thresholds on numeric rating scales (pain rating: NRS 0–10; temperature rating: NRS −10 to +10, see above). The mean ratings for three consecutive measurements each of temperature and pain during the testing of thermal pain thresholds were calculated (Wasner and Brock, 2008).

Furthermore, pain patients were asked to characterize the quality of thermally induced pain by choosing descriptors from the modified short-form McGill Pain Questionnaire or by using their own words when the thermally induced pain quality was not represented by any of the given descriptors (see above).
If thermal stimulation induced no pain within the cut-off limits, but some other sensation, pain patients were asked to indicate the temperature at which these sensations were induced and to report their quality. To ensure their validity, the thermally induced sensations needed to be reproduced in three consecutive measurements.

**Chemical activation and sensitization of small fibre afferents**

Small fibre afferents were chemically activated and sensitized by 1-menthol, histamine and capsaicin, in sequential applications. All drugs were topically applied within the skin area of below-level pain and corresponding sites in pain-free SCI patients and healthy controls. In all pain patients, the area of below-level pain was large enough to allow a distance of at least 15 cm between each site of drug application. The time between each drug application was about 30–45 min including 10–15 min time for the patient to rest before the next session.

**Menthol**

Topical menthol activates and sensitises peripheral cold C fibre nociceptors and non-noxious cold-specific A delta fibre afferents via TRPM8, a menthol- and cold-sensitive ion channel of the transient-receptor potential family (Wasner et al., 2004). A 0.7 ml aliquot of a solution containing 400 mg/ml of 1-menthol (40% w/v) dissolved in 90% ethanol was placed on a 3 × 3 cm² gauze pad, which was applied to the skin for 15 min. To protect the ethanol from evaporation, the gauze pad was covered with adhesive film and fixed by a 2.5 cm wide rubber band to ensure adequate contact between the solution and the skin (Wasner et al., 2004). Before and after topical menthol, mechanosensory testing and thermotesting (cold detection and cold pain thresholds, as described earlier) were performed in the same area as menthol application (Fig. 1).

**Histamine**

Cutaneous application of histamine induces an itch sensation due to activation of histamine-sensitive C-fibre afferents synapsing with a distinct neural pathway within the spinothalamic tract that mediates itch-sensations (Schmelz et al., 1997; Andrew and Craig, 2001; Schmelz, 2001).

Histamine was ionophorized intracutaneously (histamine hydrochloride 1%, charge 4.8 mC: 80 µA for 60 s) via a silver disc electrode of 0.5 cm diameter. Skin temperature, itch sensation and blood flow were evaluated before and after topical histamine (Fig. 1).

**Capsaicin**

Capsaicin strongly activates and sensitizes C nociceptors via TRPV1, a heat sensitive ion channel of the transient-receptor potential family (LaMotte et al., 1992; Baron, 2000; Caterina et al., 2000).

A 300 µl aliquot of a solution containing 0.02 M capsaicin (0.6%) dissolved in 45% ethanol was placed on a 3 × 3 cm² gauze pad, which was applied to the skin for 15 min. Because effects of capsaicin are substantially temperature-dependent, local skin temperature was clamped at 35°C with a feedback-controlled heat lamp (Baron et al., 1999; Wasner et al., 2000, 2007). To protect the ethanol from evaporation, the gauze pad was covered with adhesive film. Before and after topical capsaicin, mechanosensory testing and thermotesting (warm detection and heat pain thresholds, as described earlier) were performed in the same area as capsaicin application, except for setting baseline temperature during thermotesting at 35°C to equal skin temperature (Fig. 1).

**Drug-induced sensations**

During application of menthol and capsaicin, the subjects were instructed to rate the perceived temperature and pain sensations on numeric rating scales every minute (pain rating: NRS 0–10; temperature rating: NRS –10 to +10; see earlier) (Wasner et al., 2004).

Intensity of itch sensation due to ionophoresis of histamine was also quantified on a NRS (0–10) for 10 min by asking the subjects every minute for rating. If any of the drugs induced a sensation other than pain, temperature or itch, respectively, the subjects were asked to report the quality of this sensation (Fig. 1).

**Cutaneous vascular perfusion**

Skin temperature was measured at sites of drug application below the neurological level with an infra-red thermometer (Linear Instruments, USA). During histamine and capsaicin application, cutaneous vascular perfusion was measured non-invasively by laser Doppler flowmetry, yielding relative blood flow changes in arbitrary perfusion units (Moor Instruments, Axminster, Devon, UK). The laser Doppler probe was placed 1 cm distal to the electrode for histamine ionophoresis, and also 1 cm from the edge of the capsaicin gauze pad, for continuous measurement of skin blood flow outside the application area. Axon reflex vasodilation (relative increase in blood flow) was calculated as follows: (maximal flow after drug application—baseline flow/baseline flow × 100) (Baron and Sager, 1993). At the end of each session, the visible area of histamine- or capsaicin-evoked flare was drawn on sheets of plastic film and measured using a digital planimeter (Fig. 1).

**Data acquisition and analysis**

Because most of the measured parameters were not normally distributed (Rolke et al., 2006), data are presented as median (50th percentile) and interquartile range (25–75th percentiles), the U-test was applied for unpaired data analyses and the Wilcoxon-test for paired data analyses. Normally distributed data are presented as mean ± SE and a parametric procedure was used (Student’s t-test, see Table 3). The Chi-square test was used to test for differences in the proportions of the responses to the applied tests between the patient groups.

Statistical significance was assigned at the P ≤ 0.05 level by two-tailed analysis.

**Results**

**Subject characteristics**

In all patients, testing for touch, pinprick, vibration sense and motor function revealed the absence of sensory and motor function in the area of interest below the level of injury. The absence of sensory and motor function in the lowest sacral segment indicated a complete spinal cord lesion according to the American Spinal Injury Association’s standards for classification of SCI (ASIA, grade A) in all patients (Maynard et al., 1997) (Tables 1 and 2).
Three patients in each group had a ZPP referring to dermatomes and myotomes caudal to the neurological level that remained partially innervated. In all of these cases, this zone was well localized outside the test area (Tables 1 and 2).

Traumatic SCI was the underlying cause of the lesion in all but one patient who had suffered a spinal infarction (Tables 1 and 2). There were no differences in time since injury, distribution of neurological level and grading of spasticity between the two patient groups (Table 3).

Five patients with below-level pain suffered also from neuropathic pain at the neurological level (Table 1).

However, in all pain patients, below-level pain was the dominating symptom and was well discriminated both in quality and site of origin from their at-level pain. Three SCI patients in the pain-free group had a history of occasional at-level pain of moderate intensity that was not present during the testing period (Table 2).

All pain patients had a history of taking oral medication against neuropathic pain and six patients still received treatment. However, their medication did not provide adequate pain relief in any of the patients (Table 1).

As confirmed by MRI, two patients in each group developed posttraumatic syringomyelia, which was not

<p>| Table 1. Clinical characteristics of spinal cord injured people with central pain below the level of injury |</p>
<table>
<thead>
<tr>
<th>No</th>
<th>Age/Sex</th>
<th>Neurological level</th>
<th>ASIA</th>
<th>Time since injury (months)</th>
<th>Mechanism of injury</th>
<th>Area of below-level pain</th>
<th>Test area</th>
<th>At-level pain</th>
<th>Pain medication</th>
<th>Syrinx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/M</td>
<td>T4</td>
<td>A</td>
<td>7</td>
<td>Water skiing accident</td>
<td>Upper legs, feet</td>
<td>Feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>33/M</td>
<td>T4</td>
<td>A, ZPP (T7)</td>
<td>95</td>
<td>Bike accident</td>
<td>Legs</td>
<td>Left lower leg</td>
<td>Yes</td>
<td>C6-T5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25/M</td>
<td>T1</td>
<td>A, ZPP (T4)</td>
<td>28</td>
<td>Motor vehicle accident</td>
<td>Lower abdomen, right knee</td>
<td>Left lower abdomen</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52/M</td>
<td>T5</td>
<td>A</td>
<td>348</td>
<td>Motor vehicle accident</td>
<td>Legs</td>
<td>Left upper leg</td>
<td></td>
<td>C7-T2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>46/M</td>
<td>T5</td>
<td>A</td>
<td>322</td>
<td>Motor vehicle accident</td>
<td>Legs</td>
<td>Left lower leg</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>34/M</td>
<td>C7</td>
<td>A, ZPP (T4)</td>
<td>42</td>
<td>Diving accident</td>
<td>Left lower leg</td>
<td>Left lower leg</td>
<td></td>
<td>Gabapentin, amitriptyline</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>40/M</td>
<td>T10</td>
<td>A</td>
<td>44</td>
<td>Motor vehicle accident</td>
<td>Legs</td>
<td>Right lower leg and both feet</td>
<td>Yes</td>
<td>Gabapentin, amitriptyline</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>61/F</td>
<td>T10</td>
<td>A</td>
<td>34</td>
<td>Fall from height</td>
<td>Legs</td>
<td>Right lower leg</td>
<td>Yes</td>
<td>Gabapentin, oxycodone, amitriptyline</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>29/M</td>
<td>C7</td>
<td>A</td>
<td>53</td>
<td>Motor vehicle accident</td>
<td>Feet</td>
<td>Left lower leg and foot</td>
<td></td>
<td>Gabapentin, oxycodone, amitriptyline</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>61/M</td>
<td>T10</td>
<td>A</td>
<td>48</td>
<td>Motor vehicle accident</td>
<td>Feet and left lower leg</td>
<td>Right upper leg</td>
<td></td>
<td>Pregabalin</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>57/M</td>
<td>T7</td>
<td>A</td>
<td>384</td>
<td>Motor vehicle accident</td>
<td>Feet</td>
<td></td>
<td></td>
<td>Pregabalin, amitriptyline</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>29/M</td>
<td>T4</td>
<td>A</td>
<td>34</td>
<td>Motor vehicle accident</td>
<td>Feet</td>
<td>Left foot</td>
<td>Yes</td>
<td>Pregabalin, amitriptyline</td>
<td></td>
</tr>
</tbody>
</table>

Loss of sensory and motor function in the lowest sacral segment indicated a complete spinal cord lesion according to the ASIA, grade A in all patients (Maynard et al., 1997). Three patients had a ZPP referring to dermatomes and myotomes caudal to the neurological level (in brackets) that remains partially innervated.

<p>| Table 2 Clinical characteristics of spinal cord injured people without pain below the level of injury |</p>
<table>
<thead>
<tr>
<th>No</th>
<th>Age/Sex</th>
<th>Neurological level</th>
<th>ASIA</th>
<th>Time since injury (months)</th>
<th>Mechanism of injury</th>
<th>At-level pain</th>
<th>Syrinx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39/M</td>
<td>T5</td>
<td>A</td>
<td>72</td>
<td>Motor vehicle accident</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22/M</td>
<td>T4</td>
<td>A</td>
<td>12</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>T4</td>
<td>A</td>
<td>39</td>
<td>Motor vehicle accident</td>
<td>Yes</td>
<td>T2-T3</td>
</tr>
<tr>
<td>4</td>
<td>61/M</td>
<td>T4</td>
<td>A</td>
<td>450</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35/M</td>
<td>C6</td>
<td>A</td>
<td>20</td>
<td>Diving accident</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>38/M</td>
<td>T5</td>
<td>A, ZPP (T8)</td>
<td>18</td>
<td>Spinal infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>36/M</td>
<td>T9</td>
<td>A</td>
<td>226</td>
<td>Motor vehicle accident</td>
<td></td>
<td>T6-T9</td>
</tr>
<tr>
<td>8</td>
<td>60/M</td>
<td>C4</td>
<td>A, ZPP (C7)</td>
<td>502</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>30/M</td>
<td>T7</td>
<td>A, ZPP (L2)</td>
<td>50</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>67/M</td>
<td>T10</td>
<td>A</td>
<td>93</td>
<td>Fall from height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>44/M</td>
<td>T7</td>
<td>A</td>
<td>327</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>46/M</td>
<td>T8</td>
<td>A</td>
<td>215</td>
<td>Motor vehicle accident</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients were classified ASIA grade A as described in the text. Three patients had a ZPP referring to dermatomes and myotomes caudal to the neurological level (in brackets) that remains partially innervated in complete patients.
accompanied by any change in the symptoms below the neurological level (Tables 1 and 2).

**Sensation in control areas above the neurological level**

None of the subjects experienced any spontaneous ongoing sensation in the facial area which served as the control area above the neurological level of the lesion. Quantitative sensory testing in the face revealed no significant differences in perception of mechanical or thermal stimuli and pain thresholds between SCI patients with and without pain and healthy controls (Fig. 2).

**Neuropathic pain below the neurological level**

All SCI pain patients suffered from ongoing pain with a median pain intensity scored as NRS 5 (interquartile range NRS 3–6.8) (Table 4). Burning was the predominant pain descriptor chosen by 9 out of 12 patients; other pain characteristics included stinging, dull, aching, heavy, shooting and sharp. Interestingly, only three patients described the pain as hot-burning with a median temperature intensity of NRS 5 (interquartile range NRS 4–8) whereas, in eight patients, the pain was not accompanied by any temperature component irrespective of whether the pain was characterized as burning. One patient described pain as an ongoing cold aching sharp sensation with an intensity of NRS 5 and a temperature component of NRS −5 (Table 4, no. 8).

None of the pain patients suffered from any kind of evoked pain below the neurological level. None of the SCI control patients or the healthy control subjects suffered from any ongoing sensation or any evoked pain below the neurological level.

**Sensations induced by activation and sensitization of small fibre afferents below the neurological level**

**SCI people**

Mechanical stimulation with von Frey hairs or by moving a cotton swab within the area of below-level pain and within the corresponding pain-free area in SCI control patients did not induce any sensation in the people with SCI in accord with the clinical diagnosis of complete SCI. Thermal stimuli between 0°C and 50°C did not induce any sensation in either patient group except for two SCI pain patients. In patient no. 3, an average heating temperature of 48.7°C of three consecutive stimuli led to a sensation of shooting pain with an intensity of NRS 2 (Table 4). The same kind of shooting pain (underlined in Table 4) with an intensity of NRS 3 was one of the pain descriptors chosen by this patient to characterize his neuropathic pain. In patient no. 8, skin cooling to a temperature of 26.1°C led to an intense cold sensation rated with NRS −6. As described earlier, coldness (underlined in Table 4) was one of the major pain characteristics in this patient. Therefore, in both these patients, thermal stimulation rekindled characteristics typical of their individual neuropathic pain sensations.

Chemical activation and sensitization of small fibre afferents by topical application of menthol, histamine or capsaicin did not induce any sensation in either of the two SCI patient groups. However, thermal heat (but not mechanical or cold stimulation) after sensitization with capsaicin evoked sensations in six additional SCI pain patients rekindling typical individual neuropathic pain characteristics (Table 4). In four of these patients (Table 4, nos. 1, 2, 4 and 5), heat stimuli of certain intensities induced painful sensations sharing at least one quality of their neuropathic pain sensations (underlined in Table 4). In two patients (nos. 6 and 7), who described their neuropathic pain as hot, thermal stimulation after capsaicin rekindled this temperature component by inducing non-noxious warm sensations within the painful area.

In four pain patients (Table 4, nos. 9–12), as well as in all pain-free control SCI people, neither thermal nor mechanical stimuli evoked any sensation after sensitization of small fibre afferents. The pain characteristics of these four SCI pain patients (burning, hot-burning, sharp, stinging, aching and tingling) did not differ from those of the SCI people with thermally evoked pain sensations.

**Table 3** Group data on clinical characteristics of the three study groups of each 12 subjects

<table>
<thead>
<tr>
<th></th>
<th>SCI with pain</th>
<th>SCI without pain</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.8 ± 14.2</td>
<td>43.6 ± 13.4</td>
<td>377 ± 12.8</td>
<td>NS*&lt;#1</td>
</tr>
<tr>
<td>Time since injury (months)</td>
<td>120 ± 142</td>
<td>169 ± 175</td>
<td>9/3</td>
<td>NS*&lt;#1</td>
</tr>
<tr>
<td>Male/female</td>
<td></td>
<td>12/10</td>
<td></td>
<td>NS*&lt;#1</td>
</tr>
<tr>
<td>Neurological level cervical/thoracic</td>
<td>2/10</td>
<td>2/10</td>
<td>0</td>
<td>NS&lt;0.001&lt;#1</td>
</tr>
<tr>
<td>Spasm frequency scale</td>
<td>2.8 ± 1.3</td>
<td>2.7 ± 1.5</td>
<td>0</td>
<td>NS&lt;0.001&lt;#1</td>
</tr>
<tr>
<td>Modified Ashworth Scale</td>
<td>1 ± 0.6</td>
<td>1 ± 0.8</td>
<td>0</td>
<td>NS&lt;0.001&lt;#1</td>
</tr>
</tbody>
</table>

Spasticity was assessed using the spasm frequency scale [ranging from 0 (no spasms) to 4 (>10 spasms per day); Snow et al., 1990] and the modified Ashworth Scale [ranging from 0 (no increase in tone) to 4 (two people required to abduct the hips to 45°); Bohannon and Smith, 1987].

*SCI with pain versus SCI without pain.
*SCI with pain versus controls.
‡SCI without pain versus controls; data are presented as mean ± SEM.
In summary, 8 out of 12 SCI people with neuropathic below-level pain responded to thermal stimulation in the painful area either before or after chemical sensitization of small fibre nociceptive afferents, whereas there were no responders in the control group of pain-free SCI people (P < 0.001; C31 test).

Control subjects

In healthy controls, thresholds for mechanical and thermal stimuli prior to sensitization of small fibre afferents were all within normal limits as described in other studies on quantitative sensory testing (Fig. 3) (Rolke et al., 2006).

Topical application of menthol induced an ongoing cold sensation rated with an intensity of NRS –3 (median; interquartile range: NRS –0.4 to –4), a moderate pain sensation present in only 3/12 subjects (median NRS 0; interquartile range: NRS 0–0.4) and significant cold allodynia (Fig. 3A). Punctate hyperalgesia was found in only 6/12 subjects measuring 9.6 cm² (median; interquartile range 6.4–19.9). Dynamic mechanical allodynia was not present in any subject after menthol.

Ionophoresis of histamine induced an ongoing itch sensation in all subjects of moderate intensity (NRS 0–10; median NRS 2; interquartile range NRS 1.1–4.8).

Topical application of capsaicin induced an intense ongoing hot burning sensation [NRS 6 (median; interquartile range 4–8) for temperature and NRS 7.3 (median; interquartile range 6–8.8) for pain] as well as punctuate and heat hyperalgesia (Fig. 3B). Areas of punctuate hyperalgesia in 10/12 subjects measured 27.3 cm² (median; interquartile range 21.7–37.8). Dynamic mechanical allodynia was present in 10/12 subjects and measured 18.4 cm² (median; interquartile range 15.2–23.2).

In summary, results on quantitative sensory testing in combination with drug-induced activation and sensitization of small fibre afferents in intact healthy controls were in accord with previously published data (Baron and Saguer, 1993; Wasner et al., 2000, 2004; Rolke et al., 2006).

Cutaneous vascular perfusion

Skin temperature and blood flow prior to histamine ionophoresis was not significantly different between SCI patients and control subjects (Fig. 4A and B). However, both blood-flow increase and flare size induced by histamine were significantly larger in healthy controls compared to the two patient groups (Fig. 4C and D). There were no differences between SCI patients with and without below-level pain. Histamine-induced axon reflex vasodilation did not differ between SCI pain patients in whom neuropathic pain sensations were rekindled by heat stimuli prior to or after capsaicin-sensitization (Table 4, nos. 1–7) and pain patients who did not respond to heat (Table 4, nos. 8–12) (Fig. 4C and D).

During capsaicin application, skin temperature was held at 35°C. Baseline blood flow was not significantly different between the three subject groups (Fig. 5A). There was a trend towards larger increases in blood flow and flare size after capsaicin in healthy controls as compared to the two patient groups but this did not reach statistical significance (Fig. 5B and C, P = 0.18). However, within the group of patients with central pain, the increases in blood flow of people who developed pain in response to heat stimuli before or after capsaicin (Table 4, nos. 1–7) were significantly larger than those in pain patients who did not respond to heat (Table 4, nos. 8–12, P < 0.05) and reached values similar to those in healthy controls (Fig. 5B). A similar trend was present in the size of the capsaicin-induced flare (Fig. 5C; P = 0.11). Blood flow and flare size of SCI pain patients who did not respond to capsaicin resembled those in pain-free patients (Fig. 5B and C).
Table 4 Characteristics of below level pain and thermally induced sensations in each spinal cord injured patient with central pain

<table>
<thead>
<tr>
<th>No</th>
<th>Characteristics of below level pain</th>
<th>Thermally induced sensations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain descriptors</td>
<td>Threshold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evoked sensations</td>
</tr>
<tr>
<td>1</td>
<td>Burning, stinging</td>
<td>48.1 (Capsaicin)</td>
</tr>
<tr>
<td>2</td>
<td>Burning, sharp, pins and needles</td>
<td>39.0 (Capsaicin)</td>
</tr>
<tr>
<td>3</td>
<td>Dull, shooting, squeezing</td>
<td>48.7</td>
</tr>
<tr>
<td>4</td>
<td>Dull, heavy, tight</td>
<td>40.2 (Capsaicin)</td>
</tr>
<tr>
<td>5</td>
<td>Burning, unpleasant tingling</td>
<td>49.5 (Capsaicin)</td>
</tr>
<tr>
<td>6</td>
<td>Hot-burning, tingling</td>
<td>47.8 (Capsaicin)</td>
</tr>
<tr>
<td>7</td>
<td>Hot-burning, aching</td>
<td>40.5 (Capsaicin)</td>
</tr>
<tr>
<td>8</td>
<td>Cold, aching, sharp</td>
<td>26.1</td>
</tr>
<tr>
<td>9</td>
<td>Hot-burning, sharp, cramping</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Burning, stinging, tingling</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Burning, aching, tingling</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Burning, dull</td>
<td></td>
</tr>
</tbody>
</table>

Patients characterized quality of their below-level pain and of thermally induced sensations by descriptors chosen from a modified short-form McGill Pain Questionnaire or by using their own words in case the pain quality was not represented by any of the given descriptors (Wasner et al., 2002). Average pain intensity and the average intensity of any temperature component accompanying the pain was rated on numeric rating scales (pain rating: NRS 0–10, 0 = no pain; 10 = maximum pain; temperature rating: NRS –10 to +10; –10 = maximum cold; 0 = neutral temperature sensation; +10 = maximum heat). Thermal thresholds at which evoked sensations were perceived are given. In six subjects heat stimulation evoked sensation only after capsaicin (in brackets), whereas in two subjects (no. 3 and 8) thermal stimulation alone was effective. Note that thermally evoked sensations rekindled typical characteristics of the patients’ individual neuropathic pain sensations (underlined descriptors). In four pain patients (no. 9–12) no sensation was induced.

Discussion

The present study has revealed persisting spinothalamic tract function in the majority of patients with central pain following clinically complete SCI. Thermal stimulation after topical activation and sensitization of peripheral small fibre (mainly nociceptive) afferents in the area to which pain was referred evoked sensations in 8/12 cases. The thermally evoked sensations mimicked the characteristics of each patient’s individual pain implying that these residual connections were involved in pain generation. No sensations were induced in matched pain-free patients given the same protocol. We conclude that partially preserved spinothalamic tract pathways can be the site of the ‘central pain generator’ after spinal cord injuries.

Several previous studies using quantitative sensory testing including thermal stimulation in patients with central pain have demonstrated deficits in spinothalamic tract function indicating that lesions within the ascending nociceptive pathways are essential for the development of central pain (Defrin et al., 2001; Finnerup et al., 2003, 2007; Finnerup and Jensen, 2004; Ducrèux et al., 2006; Siddall and Middleton, 2006). However, as these studies failed to show differences in disturbed spinothalamic tract function between patients with and without pain, the exact involvement of the spinothalamic tract in mediating central pain remained unclear. Our approach has enabled residual function of heat- and cold-sensitive small fibre afferents to be demonstrated. Thermal stimulation prior to and after sensitization of different classes of small fibre afferents by menthol, capsaicin and histamine was the pivotal methodological approach that enabled us to identify the differences between patients with and without central pain.

‘Discomplete’ sensory lesions of spinothalamic tract in central pain patients

In our experiments, sensations were evoked in two-thirds of the SCI patients with pain, but in none of the patients without pain. Two pain patients responded to thermal stimuli even before peripheral sensitization, which is in accord with the previous data showing that sensations can be evoked below the lesion in a minority of people classified as having complete SCI (Finnerup and Jensen, 2004). However, in the other six responders, sensations could be elicited by heat stimuli but required sensitization of nociceptive afferents with capsaicin. In these cases, the stimuli were extremely strong and not in the range tolerated by the able-bodied control subjects.

It is unlikely that our findings are biased by the psychophysical nature of the methods, because (i) the patients identified the exact site of the stimulus without seeing it being applied and (ii) thresholds were reproducible during repetitive stimulation. In addition, the psychophysical approach cannot account for the differences between patients with and without pain. Furthermore, quantitative sensory testing in the face revealed no differences between SCI patients with and without central pain and healthy controls indicating not only that small fibre afferents in this control area well above the lesion had normal function,
but also that SCI people are as competent in dealing with this methodology as able-bodied controls.

Preserved sensations following peripheral stimulation of thermosensory afferents can only be explained by a ‘discomplete’ lesion within the spinothalamic tract that left residual connections between the skin site where central pain was perceived and the brain. As such discomplete lesions were not detected in the group of comparable SCI patients without below-level pain, these partially preserved pathways could be involved in the development of central pain.

The concept of discomplete SCI was first introduced to describe clinically complete lesions accompanied by neurophysiological evidence of residual brain influences on spinal motor function below the lesion (Dimitrijevic, 1988; Sherwood et al., 1992). Later, the term ‘sensory discomplete’ was used to describe a minority of people classified by clinical criteria as having complete SCI but in whom sensations could be evoked from below the lesion (Finnerup and Jensen, 2004). The present study demonstrates that many subjects with pain arising below the SCI can be considered to have similarly discomplete lesions of their spinothalamic pathways.

**Which spinothalamic tract neurons are preserved in central pain patients?**

Several mechano- and thermosensitive afferents can be activated by quantitative sensory testing in conjunction with...
with topical drug application as data from healthy controls demonstrate. Menthol and capsaicin induced ongoing pain, thermal and mechanical hyperalgesia due to sensitization of cold and heat-specific nociceptive afferents (LaMotte et al., 1992; Baron, 2000; Wasner et al., 2004; Namer et al., 2005). Histamine induced a prolonged itch sensation due to activation of histamine-sensitive afferents (Schmelz et al., 1997; Andrew and Craig, 2001; Schmelz, 2001).

The fact that the majority of our spinothalamic incompletely central pain patients responded to heat after capsaicin, whereas none of the other potenti thermal or mechanical stimuli evoked in them any sensation, implies that only a subset of spinothalamic tract pathways was preserved. These intact fibres must have been capsaicin-in sensitive as well as heat-sensitive, because stimulation with capsaicin alone was not potent enough to induce any sensation, as was demonstrated in a previous study (Finnerup et al., 2007a). Capsaicin acts on two subpopulations of C fibre nociceptors via TRPV1, the transient-receptor potential cation channel V1 (Szolcsanyi, 2004). Activation and sensitization of mecha nosensitive nociceptors encode long-lasting capsaicin-induced burning pain, heat hyperalgesia and flare responses, whereas polymodal nociceptors are activated only briefly by capsaicin and do not appear to be sensitized (Schmelz et al., 2000; Schmidt et al., 2000). As mecha nosensitive nociceptors respond not only to capsaicin, but also to heat, their activation may also account for the sensations induced by heat stimuli prior to capsaicin application in one SCI pain patient. Therefore, we suggest that a subset of spinothalamic tract neurons which receive inputs from mechathe insensitive C fibre nociceptors was partially preserved in these central pain patients.

This hypothesis is supported by data presented here on drug-elicted axon reflexes. The axon reflex vasodilation is due to release of vasoactive peptides (substance P and mainly calcitonin gene-related peptide, CGRP) from the endings of small fibre afferents (Szolcsanyi, 2004). Capsaicin and histamine evoked reduced axon reflex vasodilation in both patient groups compared to healthy controls as previously demonstrated (Finnerup et al., 2007a). It was suggested (Kuesgen et al., 2002) that this may be due to increased vasoconstriction following injury-related changes in sympathetic efferent activity counteracting axon reflex vasodilation. However, as skin temperature and baseline blood flow were not different between the groups, no direct evidence for such a mechanism has been found in the present study. Notably, however, capsaicin induced a significantly larger blood-flow increase in the SCI pain patients who responded to heat before or after capsaicin than in pain patients who did not respond (Fig. 5B). This difference was specific for capsaicin-sensitive axons because there was no difference between the histamine-induced axon reflexes which involves different axons. As it is suggested that dorsal root reflexes via spinal pathways including the dorsal horn are involved in axon reflex vasodilation (Lin et al., 1999; Weng and Dougherty, 2005), these data suggest that the pathways from mecha insensitive nociceptors were more preserved in these patients than in non-responders. CGRP-containing afferent axons have been reported to sprout in the dorsal horn of many segments above and below both transection (Krenz and Weaver, 1998) and severe compression of rat spinal cord (Weaver et al., 2001) and have been proposed to play a role in development of central pain (Christensen and Hulsebosch, 1997). Whether such sprouting axons are CGRP-containing mechanosensitive nociceptive afferents is not clear.

Apart from the involvement of the dorsal horn in axon reflexes, the lack of drug-induced vasodilation in the non-responders and in the patients without central pain implies that central lesions can affect the function or even anatomical integrity of primary peripheral nociceptors that are not directly damaged. One can speculate that uninjured nociceptive afferents below the injury lose their expression of vasodilator peptides, their excitability or even that they degenerate. There might be retrograde transneuronal degeneration after damage to the secondary spinothalamic afferents, as occurs in the visual system where undamaged retinal ganglion cells degenerate after striate cortical lesions in primates (Cowey, 1974; Johnson and Cowey, 2000).

One of the eight SCI responders with central pain reacted to cooling, but not to heating (Table 4, no. 8),
indicating that the preserved spinothalamic pathways in this patient were connected not with mechano-insensitive C fibre nociceptors but with cold-specific afferents (Wasner et al., 2004).

**Are intact spinothalamic tract neurons the site of the ‘spinal pain generator’?**

In all eight central pain patients that responded to peripheral thermal stimuli, the evoked pains had characteristics typical of their individual spontaneous pain sensations (Table 4), i.e. their neuropathic pain was rekindled. This indicates that central pain is at least partly driven by the pathological activity of preserved spinothalamic afferents and suggests that they act as ‘spinal pain generators’.

The idea that activity in uninjured fibres contributes to neuropathic pain comes from animal studies demonstrating ongoing discharge of uninjured C fibres in a peripheral nerve trunk containing degenerating axons (Wu et al., 2001; Djouhri et al., 2006). It is thought that inflammatory mediators such as cytokines (e.g. tumour necrosis factor-alpha) and neurotrophic factors (nerve growth factor) released from non-neuronal cells around neighbouring degenerating axons are the key players for eliciting pathological activity in intact afferents (Wu et al., 2001; Schafers et al., 2003; Djouhri et al., 2006; Scholz and Woolf, 2007). Similar inflammatory changes in the injured spinal cord are not restricted to the injury site and the surrounding region of secondary degeneration but extend along the spinal cord rostral and caudal to the lesion, with activation of microglia (Popovich et al., 1997; McKay et al., 2007; Donnelly and Popovich, 2008) persisting for over a year, as post-mortem studies in humans have demonstrated (Schmitt et al., 2000). Microglial activation in both the dorsal horn and thalamus after experimental SCI is associated with pain-related behaviour as well as increased hyperexcitability and upregulation of Nav1.3 channels in nociceptive neurons (Hains and Waxman, 2007). Remote activation of microglia with increases in pro-inflammatory cytokines has been shown to predict the onset and severity of below-level neuropathic pain after incomplete SCI in rats (Detloff et al., 2008). However, it is not clear whether such inflammatory processes are capable of maintaining chronic pain for years, in particular as animals have rarely been studied for longer than 1 month after injury. It is possible that inflammatory processes initiate a cascade of functional or structural changes which trigger chronic ectopic activity in nociceptive pathways.

**Where is the ‘pain generator’ located?**

The present data indicate that central pain can be induced by activity in intact spinothalamic afferents located in the dorsal horn where inflammatory processes are prominent (Hains and Waxman, 2006; McKay et al., 2007; Detloff et al., 2008) and ascending spinothalamic tract neurons are located (Saab et al., 2008). Degeneration of some spinothalamic tract neurons with axons injured at the level of the lesion (Fig. 6, encircled 1) could be responsible for microglial activation around the surviving spinothalamic neurons triggering excitation. In addition, spinal lesions will interrupt descending inhibitory pathways arising from the brainstem (Fig. 6, encircled 2) that play a crucial role in modulating the excitability of dorsal horn neurons (Meller and Gebhart, 1993). Hyperexcitability of these neurons located far below the level of the injury may then be the basis of the ‘spinal pain generator’ (Fig. 6).

It is also possible that spontaneous activity in residual spinothalamic pathways originates from ascending spinothalamic tract axons within the white matter particularly close to the site of the lesion (Fig. 6, encircled 3). Inflammation in the white matter is characterized by persistent CD68+ macrophages involved in the prolonged

---

**Fig. 6** Proposed role of residual spinothalamic tract neurons in below-level pain following SCI. SCI (grey bar) lesioned the majority of spinothalamic tract axons (dashed think line) leading to retrograde reactions (possibly degeneration) of the corresponding dorsal horn neurons (shaded circle). Residual spinothalamic afferents, which were not affected by the lesion (solid thin line), developed ongoing activity contributing to central neuropathic pain. Pathological activity may arise from intact dorsal horn neurons (filled circle) due to inflammatory processes associated with degeneration of neighbouring axon terminals and neurons in the dorsal horn (1), as a result of disinhibition due to lesion of descending pain inhibitory pathways (dotted line) following SCI (2). From ascending spinothalamic tract axons within the damaged white matter close to the lesion (3). Changes of excitability and discharge patterns in thalamic neurons may be triggered by ongoing activity in these intact spinothalamic afferents (4).
phagocytosis of myelin (Schmitt et al., 2000; McKay et al., 2007).

**Alternative central pain mechanisms**

There is evidence that other mechanisms can also lead to central pain (Finnerup and Jensen, 2004). In the present study, four of the pain patients did not respond to peripheral stimulation. Clinical characteristics, pain descriptors and pain intensities did not distinguish between responders and non-responders in our group of pain patients (Table 4). It may have been that the chemical stimulation was not intense enough to demonstrate any residual spinothalamic connections. Alternatively, their pain was generated by a different mechanism. Furthermore, in the group of pain patients that responded to thermal stimuli, not all of each individual’s neuropathic pain sensations were rekindled (Table 4). Therefore, it is possible that other mechanisms in higher-order neurons are also involved.

A source of pain signals suggested by animal as well as human research is hyperexcitability leading to ectopic activity of thalamic neurons following SCI (Lenz et al., 1994; Hains and Waxman, 2007). Changes in sodium channel expression related to microglial activation following de-afferentation by degeneration of the terminals of ascending spinothalamic tract neurons are proposed to be the underlying cause of these thalamic changes (Gao et al., 2004; Hains et al., 2005; Hains and Waxman, 2007; Zhao et al., 2007). The results of the present study suggest that spontaneous activity arising from residual intact spinothalamic afferents, rather than from degeneration of their terminals in the thalamus, may be the trigger for secondary changes of excitability and discharge patterns in thalamic neurons (Fig. 6, encircled 4). This idea parallels the notion of hyperexcitability in secondary nociceptive dorsal horn neurons generated following spontaneous activity in primary afferents in peripheral neuropathic pain (Campbell and Meyer, 2006).

**Conclusions and implications**

The present study provides evidence for the first time that intact spinothalamic tract afferents projecting through a damaged region of spinal cord can contribute to central pain following SCI. It is suggested that spontaneous activity is generated in these intact neurons by excitatory substances released from microglia activated during the chronic inflammation triggered by retrograde degeneration of lesioned neighbouring neurons. Therefore, we suggest that both degeneration and preservation are important for the development of central pain, because degeneration is essential for inducing the inflammatory processes that generate neuronal hyperexcitability and activity in preserved neurons.

While other mechanisms can also be responsible for central pain, residual intact pathways may also contribute to central pain syndromes other than those that follow SCI. As well as other strategies, targeted treatment options such as anti-inflammatory drugs may be successful to abolish the generation of spontaneous activity. Data from animal experiments have already demonstrated that this might be a promising approach (Hains and Waxman, 2006).

**Acknowledgements**

We thank Danielle Burton for her excellent assistance and recruiting of the patients. We thank also Associate Professor Phil Siddall and Dr Paul Wrigley for their cooperation and support in patient recruitment. The work was supported by the Alexander von Humboldt-Foundation, the Spinal Injuries Research Centre (Prince of Wales Medical Research Institute), the National Health and Medical Research Council of Australia, the International Association for the Study of Pain (IASP collaborative research grant) and the German Ministry of Research and Education within the German Research Network on Neuropathic Pain (BMBF, 01EM 05/04).

**References**


Deflof MR, Fisher LC, McLaughey V, Longbrake EE, Popovich PG, Basso DM. Remote activation of microglia and pro-inflammatory...
cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats. Exp Neurol 2008 [Epub ahead of print].


Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. Brain 2003; 126: 57–70.


LaMotte RH, Lundberg LE, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C-units in humans after intraarticular injection of capsaicin. J Physiol (Lond) 1992; 448: 749–64.

