Pain 210 (2006) 145–154

PAIN

www.elsevier.com/locate/pain

A PET activation study of brush-evoked allodynia in patients with nerve injury pain

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Received 6 January 2005; received in revised form 25 October 2005; accepted 31 October 2005

Abstract

Acute experimental brush-evoked allodynia induces a cortical activation pattern that differs from that typically seen during experimental nociceptive pain. In this study, we used positron emission tomography to measure changes in regional cerebral blood flow (rCBF) in patients with clinical allodynia. Nine patients with peripheral nerve injury were scanned during rest, brush-evoked allodynia, and brushing of normal contralateral skin. PET data were analyzed for the whole group and for single subjects. Allodynic stimulation activated the contralateral orbitofrontal cortex (BA 11) in every patient. Whereas normal brushing activated most strongly the contralateral insular cortex, allodynic brushing produced an ipsilateral activation in this area. Another important difference between normal and allodynic brushing was the absence of a contralateral primary somatosensory cortex (SI) activation during allodynic brushing. No thalamic activation was observed during allodynic or control brushing. Although no anterior cingulate cortex (ACC) activation could be demonstrated in the group analysis, single subject analysis revealed that four patients activated this region during brush-evoked allodynia. A direct post hoc comparison of brush -and allodynia-induced rCBF changes showed that allodynia was associated with significantly stronger activations in orbitofrontal cortex and ipsilateral insula whereas non-painful brushing more strongly activated SI and BA 5/7. These findings indicate that activity in the cortical network involved in the sensory-discriminative processing of nociceptive pain is downregulated in neuropathic pain. Instead, there is an upregulation of activity in the orbitofrontal and insular cortices, which is probably due to the stronger emotional load of neuropathic pain and higher computational demands of processing a mixed sensation of brush and pain.

Keywords: Allodynia; Neuropathic pain; Sensory testing; Functional brain imaging; Reorganization; Orbitofrontal cortex

1. Introduction

Under normal physiological conditions, noxious stimulation activates brainstem areas, contralateral thalamus, primary and secondary somatosensory cortex (SI and SII), insula and the ACC (Casey et al., 1996; Coghill et al., 1999; Svensson et al., 1998). These areas are believed to play an important role in the sensory-discriminative and cognitive aspects of pain processing. Peripheral nerve injury induces hyperexcitability of the peripheral nervous system and spinal cord (LaMotte et al., 1991; Simone et al., 2004) with sensory perception changes and spontaneous pain. Functional brain imaging studies have shown that the default pain-induced brain activation pattern is altered under experimental or clinical hyperalgesic conditions such as capsaicin-induced allodynia (Baron et al., 1999; Iadarola et al., 1998; Witting et al., 2001) and peripheral or central nerve injury pain

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0304-3959/$20.00
doi:10.1016/j.pain.2005.10.034

(Petrovic et al., 1999; Peyron et al., 1998; 2004). We (Witting et al., 2001) and others (Baron et al., 1999; Iadarola et al., 1998) have shown that capsaicin-induced allodynia produces a unique pattern of increased activity in the prefrontal and posterior parietal (BA 5/7) cortex with unaltered activity in primary recipient zones of spinal input such as the thalamus, SI and ACC, suggesting that brain activity patterns not just passively reflect hyperexcitability at peripheral levels.

One would expect that more permanent lesions of the peripheral or central nervous system are likewise associated with a similar altered cerebral response pattern. However, the sparse available data are equivocal, some reports describing a different cerebral activation pattern (Peyron et al., 1998; 2004), others a pattern close to that observed in conditions of normal physiological pain (Hsieh et al., 1995; Petrovic et al., 1999). A possible reason for the discrepancy between the results of studies on experimental and clinical forms of allodynia is that they used different experimental procedures. Another possibility is that clinical allodynia studies used patient populations with heterogeneous pain pathology and lacked detailed quantitative sensory information. The aim of this study was therefore to investigate the cerebral response pattern in a homogeneous group of patients with allodynia following peripheral nerve injury, using identical methodological procedures for evoking allodynia as in our earlier study of capsaicin-induced allodynia. In addition, detailed quantitative sensory testing (QST) was carried out.

Neuropathic pain is an ego-dystonic type of sensation, which is difficult to describe except for the fact that it is very unpleasant and different from any other type of pain that the patient had experienced before. It often consists of a mixture of constant ongoing pain and stimulus-evoked pain (Jensen & Baron, 2003; Jensen et al., 2001). Therefore, we hypothesized that neuropathic pain will recruit brain structures involved in the encoding of coincident sensory input and in emotional processing, such as the ACC and the prefrontal and posterior parietal cortices. Part of this study has been presented in abstract form (Witting et al., 2002).

2. Materials and methods

2.1. Subjects

Nine patients (6 men and 3 women) with an average age of 52 years (range 34–78) participated in the study after given informed verbal and written consent. All participants had long-standing clinical brush-evoked allodynia following upper or lower extremity traumatic nerve injury. The study was approved by the local ethics committee of Aarhus County and was conducted in accordance with the Helsinki II declaration.

2.2. Medical history and clinical examination

A medical history with detailed information on pain was obtained in all patients. Five patients were treated with non-steroidal anti-inflammatory or mild opioid drugs that were stopped at least 12 h before sensory examination or scanning. One patient continued with acetylsalicylic acid as a prophylactic antitrombotic agent and two participants were treated with tricyclic antidepressants that were stopped at least one week before examination. Finally, one patient continued with the intake of a selective serotonin reuptake inhibitor, which originally was prescribed because of depressive symptoms.

All participants completed the Danish version of the McGill Pain questionnaire (Drewes et al., 1993). In addition, they rated ongoing and evoked pain on a 100 mm visual analogue scale (VAS, 0 = no pain, 100 = most intense pain).

2.3. Quantitative sensory testing (QST)

The QST was carried out in the area of maximal tolerable brush-evoked allodynia and in the contralateral mirror area. All measurements were done in the same order by the same examiner (NW) in a quiet room at ambient room temperature.

The test stimuli were applied to the same skin area and were not moved between trials because some of the nerve-injured areas were small. Adaptation or sensitization may therefore have influenced the QST results. However, these factors should affect the QST data of all subjects to the same extent. Moreover, the main focus of this study was to investigate the relationship between sensory characteristics and rCBF increases.

2.3.1. Brush-evoked allodynia

Allodynia was evoked by a handheld soft hairbrush that was moved along the skin at a speed of one stroke per 4 s, stimulating an area of about 2 cm^2 (0.5×4 cm; brush-velocity of 0.7 cm/s, approximate force applied of 0.15–0.20 N/cm^2). The participants rated the evoked pain continuously on an electronic VAS.

2.3.2. Thermal sensitivity

Heat and cold detection thresholds (HDT, CDT) and heat and cold pain thresholds (HPT, CPT) were determined with a thermotester (Somedic AB, Sweden) using the method of limits. The baseline temperature was set at 30 °C and the temperature change rate at 1 °C/s. Thresholds were determined as the average of five measurements with 3 s interstimulus interval.

2.3.3. Tactile sensitivity

Tactile detection thresholds (TDT) and tactile pain thresholds (TPT) were measured with von Frey filaments (Semmes-Weinstein monofilaments, Stoelting, IL, USA) applied to the skin in ascending order.

2.3.4. Temporal summation

Temporal summation was evoked, as described previously (Gottrup et al., 2003), by repetitively tapping the skin with a von Frey hair (125.9 g = 1236 mN) driven by a computer-controlled solenoid at a rate of 2 Hz for 1 min or until pain became intolerable. Patients rated evoked pain continuously on an electronic VAS.