Differential endogenous pain modulation in complex-regional pain syndrome

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Endogenous pain modulation may provide facilitation or inhibition of nociceptive input by three main mechanisms. Firstly, modification of synaptic strength in the spinal dorsal horn may increase or decrease transmission of nociceptive signals to the brain. Secondly, local dorsal horn interneurons provide both feed-forward and feed-back modulation to spinothalamic and spinobulbar projection neurons. Thirdly, descending systems originating in the brainstem exert top-down modulation of nociceptive input at the spinal level. Not much is known on the activity of these systems in complex regional pain syndrome (CRPS). CRPS is a chronic pain condition characterized by burning pain and abnormalities in the sensory, motor and autonomous nervous system. In the present study, we tested changes in endogenous pain modulation in 27 CRPS patients compared with age-matched healthy controls. We applied repetitive noxious electrical stimuli (stimulation frequency 1 Hz) at the dorsal aspect of affected and unaffected hands in patients and to corresponding hands in controls. As known from previous studies this protocol simultaneously activates inhibitory and facilitatory pain modulating systems. This results in adaptation to the repetitive noxious stimulus, and simultaneously and at the same site, in development of an area of pinprick hyperalgesia. We measured (i) pain adaptation during the course of stimulation and (ii) the provoked area of pinprick hyperalgesia. These parameters were used as activity measures of pain inhibitory and pain facilitatory systems. As both measures result from gross inhibitory and gross facilitatory activity in pain modulatory systems, pain adaptation reflects net pain inhibition and area of pinprick hyperalgesia net pain facilitation. We found (i) decreased adaptation to painful electrical stimuli on both affected and unaffected hands of CRPS patients compared to healthy controls and (ii) increased areas of hyperalgesia on affected hands of CRPS patients compared to unaffected hands of CRPS patients and healthy controls. These findings imply a shift from inhibition towards facilitation of nociceptive input in CRPS patients, based on differential activation of subcomponents of the endogenous pain modulatory system. The differences were not correlated with duration of the disease, pain intensity, autonomic or motor function scores, presence or degree of evoked pain. However, significant correlation was found with the extent of adaptation and hyperalgesia on the unaffected hand. Thus, we hypothesize that differential activity in endogenous pain modulating systems may be not only a result of CRPS, but a potential risk factor for its development.

Keywords: descending pain control; pain modulation; CRPS; RSD; neuropathic pain; electrical model; hyperalgesia; allodynia; inhibition; facilitation; brainstem

Abbreviations: AA = adaptation affected hand; AU = adaptation unaffected hand; CRPS = complex regional pain syndrome; EDT = electrical detection threshold; EPT = electrical pain threshold; HAA = hyperalgesic area affected hand; HAU = hyperalgesic area unaffected hand; LDI = laser Doppler imaging; LTD = long-term depression; LTP = long-term potentiation; MDT = mechanical
Introduction

Individual differences in endogenous pain modulation are discussed as a risk factor for the development of chronic pain (Edwards, 2005). On the other hand, chronic pain states could impact on the activity or capacity of endogenous pain modulating systems. There are three known main mechanisms of endogenous pain modulation. Firstly, mechanisms of long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength in the spinal dorsal horn have been shown to result in modified transmission of nociceptive signals in animals (Sandkuhler et al., 1997; Ikeda et al., 2003, 2006; Sandkuhler, 2007). These synaptic mechanisms have also been suggested to result in increased or decreased pain perception in humans (Klein et al., 2004; Sandkuhler, 2007). LTP and LTD are ubiquitous mechanisms of synaptic plasticity. LTD phenomena within the somatosensory system have been shown to occur after conditioning stimuli of peptidergic C-nociceptor terminals and lamina I projection neurons expressing the neurokinin-1 receptor (Ikeda et al., 2003, 2006). There is evidence from human psychophysical studies that the perceptual correlate of LTD in the nociceptive system is secondary mechanical hyperalgesia (Klein et al., 2004, 2006; Lang et al., 2007). LTD phenomena can be induced by low-frequency noxious stimulation (Sandkuhler et al., 1997; Chen and Sandkuhler, 2000) and are believed to have their perceptual correlate in a decrease in pain perception mediated by the conditioned pathway (Klein et al., 2006). As a second modulatory mechanism, there are dorsal horn inhibitory interneurons that utilize GABA, glycine or opioids and provide both feed-forward and feed-back inhibition to the spinothalamic and spinobulbar projection neurons (Basbaum and Fields, 1984; Millan, 2002; Benarroch, 2008). Thirdly, descending systems originating in the brainstem can inhibit or facilitate peripheral nociceptive input in the dorsal horn. Chronic pain states may also depend on descending control that originate in the brain (Urban and Gebhart, 1999b; Pertovaara, 2000; Porreca et al., 2002; Ren and Dubner, 2002). The midbrain periaqueductal gray (PAG) and the rostroventral medulla (RVM) are key structures of the endogenous descending pain modulatory system (Basbaum and Fields, 1978, 1984). As the PAG itself has limited direct projections to the spinal cord (Sandkuhler and Gebhart, 1984), it uses the RVM as a site that projects directly to the spinal dorsal horn. Therefore, RVM is an important intermediate in pain modulation (Basbaum and Fields, 1984; Starowicz et al., 2007). Descending projections from the PAG to the RVM and from the RVM to dorsal horn neurons are thought to regulate nociceptive input at the spinal level (Proudfit and Anderson, 1975; Basbaum and Fields, 1978; Behbehani and Fields, 1979; Sandkuhler and Gebhart, 1984). This PAG to RVM dorsal horn axis seems to form the backbone of the endogenous pain modulatory outputs (Mason, 2005). Both PAG and RVM receive input from prefrontal and cingulate cortices (Valet et al., 2004), anterior insular cortex (Hardy and Leichnetz, 1981), amygdala (Gray and Magnuson, 1992) and hypothalamus (Beitz, 1982), allowing differential regulation of activity in the pain modulatory system by cognitive or affective processes (Reynolds, 1969; Akil et al., 1976; Boivie and Meyerson, 1982). However, the descending pain control system has not only an inhibitory component. It also facilitates peripheral nociceptive input (Millan, 2002). Inflammation (Kidd and Urban, 2001; Klein et al., 2005) or neuropathy (Woolf and Mannion, 1999) can induce primary or secondary hyperalgesia. Primary hyperalgesia is characterized by increased painfulness to heat and static pressure of the injured tissue (Koltzenburg et al., 1992; Schmelz et al., 2000), secondary hyperalgesia manifests with increased painfulness to pinprick stimuli in the surrounding tissues (Ziegler et al., 1999). For experimental repetitive transcutaneous electrical stimulation only secondary hyperalgesia has been shown (Koppert et al., 2001, 2005). Secondary hyperalgesia is a product of an increase in the excitability of nociceptive spinal neurons (central sensitization). Thus, descending modulation by PAG and RVM of nociceptive input is a mixture of inhibition (Ren and Dubner, 2002) and facilitation (Urban and Gebhart, 1999a; Porreca et al., 2002) with facilitation predominating in areas in secondary hyperalgesia (Vanegas, 2004). For a detailed review see Millan (2002).

Complex regional pain syndromes (CRPS) may develop after limb trauma. The disease is characterized by sensory, autonomic and motor symptoms (Stanton-Hicks et al., 1995). The leading sensory symptoms are spontaneous and evoked pain, but hyperesthesia can also occur. The autonomic dysfunctions may consist of temperature changes, trophic disturbances, skin colour changes, oedema or sweating abnormalities. Motor symptoms include paresis, tremor and dystonia (Birklein, 2005). It can be differentiated between CRPS types I and II. CRPS type I is diagnosed when there is no obvious nerve injury, whereas CRPS type II refers to cases with nerve injury (Stanton-Hicks et al., 1995; Birklein, 2005). Although the pathogenesis of the syndrome is not completely understood, there is evidence for neurogenic inflammation (Birklein et al., 2001; Weber et al., 2001), endothelial dysfunction (Schattschneider et al., 2006b), pathological sympathico-afferent coupling (Baron et al., 2002; Schattschneider et al., 2006a) and CNS changes (Janig and Baron, 2002). As a major pathophysiological aspect, the CNS changes include pain-induced neuroplasticity. Reorganization of somatotopic maps within the primary somatosensory cortex has been shown in CRPS patients by neuroimaging techniques (Maihofner et al., 2003, 2004; Pleger et al., 2005). Cortical reorganization correlates with the individual area of mechanical hyperalgesia and perceived spontaneous pain and can be reversed by treatment (Maihofner et al., 2003, 2004). Thus, CRPS is more than a pain syndrome, it is a multisystem disease with neurophysiological manifestations at all levels of the neuraxis.

However, nothing is known about disturbances in endogenous pain modulating systems in CRPS. Therefore, we performed the present study to test the hypothesis of a differential endogenous pain modulation in CRPS patients. In particular, we applied repetitive noxious electrical stimuli at the dorsal aspect of affected and unaffected hands in patients and to corresponding hands.
in controls. Based on previous studies, we chose conditioning high-current-density electrical stimuli preferably activating mechano-insensitive C-nociceptors (Schmelz et al., 2000). This paradigm has been shown to provoke (i) well controllable pain, (ii) stable areas of pinprick hyperalgesia reflecting activation of facilitatory mechanisms and (iii) activation of an endogenous naloxone-sensitive inhibitory system reducing pain and hyperalgesia (Koppert et al., 2001, 2005). In addition, it facilitates a naloxone-insensitive inhibitory system that mainly acts antihyperalgesic (Koppert et al., 2001, 2005). If endogenous pain modulation is impaired in CRPS patients these changes might reflect a pre-existing risk factor for CRPS occurrence or a result of the CPRS manifestation.

Methods

Subjects

A total of 27 patients with clinically diagnosed CRPS (9 males, 18 females, mean age 57.6 years ± 2.56) and 14 healthy age-matched controls (3 males, 11 females, mean age 52.8 years ± 3.43 years) participated in the study. The patients had to meet the current IASP diagnostic criteria for CRPS (Stanton-Hicks et al., 1995). These criteria were extended to the IASP research criteria (Harden et al., 2007) so that at least four symptoms (at least one in each category: sensory, vasomotor, sudomotor/oedema, motor/trophic) must be reported by the patient and at least one sign must be present in two or more sign categories (sensory, vasomotor, sudomotor/oedema, motor/trophic) at time of evaluation. This results in a specificity of 0.94 (Harden et al., 2007). Patients and controls had to be 18 years or older. Exclusion criteria for the controls were history of any neurological disease or chronic pain and use of analgesics during the week before the experiment. The patients and controls were informed about the procedures of the study but were unaware of the specific experimental goals. Informed consent was obtained from all participants before the experiments. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. The stimulation site was the back of the hand in all subjects.

Study design

Initially we performed (i) baseline measurements for mechanical and electrical detection and pain thresholds, followed by (ii) a 16-min equilibration phase in which the current was adapted every 2 min to a numeric rating scale (NRS) rating of 6 (NRS 0–10). Subsequently (iii) the adaptation to the repetitive stimuli was measured over 30 min. The current was constant over this time, pain ratings (NRS 0–10) were obtained every minute. After the adaptation period the (iv) measurements for mechanical detection and pain thresholds were performed again and the (v) presence and extent of an axon reflex flare was determined by laser Doppler imaging. Furthermore, the (vi) areas of experimental pinprick hyperalgesia were measured.

Assessment of pain and quantitative sensory testing for CRPS induced pinprick hyperalgesia

Spontaneous CRPS pain was quantified using the German counterpart (Stein and Mendl, 1988) of the McGill questionnaire (MPQ). Patients were instructed to fill in the MPQ (i) regarding the spontaneous pain for the time 1 h previous to the experiment and (ii) regarding the spontaneous pain averaged over the last 4 weeks. In addition, patients quantified (i) their spontaneous pain for the time 1 h previous to the experiment and (ii) their spontaneous pain averaged over the last 4 weeks on a 11-point NRS, ranging from 0 (no pain) to 10 (intolerable pain).

Induction of electrically induced hyperalgesia

Transcutaneous electrical stimulation was used to induce ongoing pain and secondary mechanical hyperalgesia as described previously (Koppert et al., 2001, 2005; Filitz et al., 2008). Briefly, two self-adhesive electrodes were mounted on the skin at 4 mm distance on the back of the hand. Monophasic, rectangular electrical pulses of 0.5 ms duration were applied via a constant current stimulator (Digitimer S7, Digitimer, Hertfordshire, UK) at 1 Hz. The current was gradually increased during the first 16 min of stimulus administration, targeting a pain rating of 6 on an 11-point numeric rating scale (NRS; 0 = no pain and 10 = maximum tolerable pain), and was then kept constant for the remaining time of the experiment. This experimental approach has been proven to provoke stable areas of secondary hyperalgesia to punctate stimuli caused by an activation of primarily mechano-insensitive C-nociceptors (Schmelz et al., 2000). This class of nociceptors was shown to be electrically activated preferentially at high current densities as used in this model (Weidner et al., 1999).

Psychophysical testing

Psychophysical testing was performed to assess the following parameters: (i) mechanical detection threshold (MDT), (ii) mechanical pain threshold (MPT), (iii) electrical detection threshold (EDT), (iv) electrical pain threshold (EPT) and (v) area of pinprick hyperalgesia. The MDT and MPT were determined before and after the stimulation period as described in detail in (Rolke et al., 2006). Briefly, MDT was measured with a standardized set of modified von Frey hairs (Optihair-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512 mN graded by a factor of 2 (1 s contact time). Using the ‘method of limits’, 5 threshold determinations were made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these five series. MPT was measured before and after electrical stimulation using custom-made weighted pinprick stimuli as a set of seven pinprick mechanical stimulators with fixed stimulus intensities that exerted forces of 8, 16, 32, 64, 128, 256 and 512 mN. Measurements were done at the site of electrical stimulation. The stimulators were applied for 12 s in an ascending order until the first perception of pain was reached. The final threshold was the geometric mean of five series of ascending and descending stimuli. The EDT and EPT were measured only before the stimulation period by slowly increasing the current until the stimulus was detected (EDT) or the first percept of pain was reached (EPT). Areas hyperalgesic to pinprick were assessed before and after the stimulation period using a 256 mN pinprick stimulator. The borders of the hyperalgesic areas were delineated by testing pinprick sensitivity along eight linear paths (separated by an angle of 45°) parallel and vertical to the axis of the hand from distant starting points towards the stimulation site (step size 0.5 cm) until the subject reported increased pain sensations evoked by the pinprick.
Laser-Doppler-imaging

We used a laser Doppler imager (LDI, Moor, London, UK) to assess the axon reflex flare in parallel to the psychophysical protocol after transcutaneous repetitive electrical stimulation as described above. A rectangular skin area around the stimulation site was scanned at a distance of 30 cm with a two-dimensional spatial resolution of 0.5 mm. Laser Doppler scans were taken three times at 10 min intervals after the stimulation period. The size of the axon reflex flare erythema was analysed offline using dedicated software (MLDI 3.8, Moor, UK). The flare area was defined as the number of pixels that had a flux value exceeding the mean flux of all pixels in the control scan (before stimulation) by 2 SDs, as described before (Namer et al., 2005).

Correlation analysis

In order to correlate the obtained adaptation curves and hyperalgesic areas with clinical parameters we calculated z-scores of (i) the electrical induced pain intensity at the end of the adaptation phase (NRS minute 46 of electrical stimulation) and (ii) the hyperalgesic area (in cm²) by calculating the z-transform: \( Z = \frac{\text{value}_{\text{patient}} - \text{mean}_{\text{group}}}{\text{SD}_{\text{group}}} \). The z-scores of (i) adaptation and (ii) hyperalgesic area were tested for correlation with (a) each other (b) the z-score of adaptation of the contralateral hand; (c) the z-score of the hyperalgesic area of the contralateral hand; (d) the CRPS duration; (e) pain intensity obtained by the numeric rating scale regarding: (1) spontaneous pain for the time 1 h previous to the experiment and (2) spontaneous pain averaged over the last 4 weeks; (f) pain intensity obtained by the pain rating index (PRI) of the German counterpart of the MPQ regarding: (1) spontaneous pain for the time 1 h previous to the experiment and (2) spontaneous pain averaged over the last 4 weeks; (g) the sum score of motor symptoms; (h) the sum score of autonomic disturbances; (i) medications used at the day of the experiment: (1) tricyclic antidepressants, (2) opioids, (3) gabapentin and pregabalin, (4) NSAID; (j) age. Pearson product moment correlation coefficient was used. Bonferroni correction for multiple testing was applied.

Statistical analysis

The data are presented as mean ± SEM. Statistical evaluation was performed using the STATISTICA software package. The data obtained from both hands of the control group were pooled together for further analysis. For analysis of MDTs and MPTs of the different groups an antilog function was applied to all individual thresholds before further statistical analysis. ANOVA with the two factors ‘group’ (levels: CRPS affected, CRPS unaffected, control) and ‘time’ (levels: pre, post) was performed. Post hoc Bonferroni test was used. For statistical analysis of the course of adaptation to the repetitive stimuli ANOVA was performed with three factors: ‘group’ (levels: CRPS, control), ‘side’ (levels: left, right, affected, unaffected) and ‘time’ (levels: 30 time points). Again, post hoc Bonferroni test was used. To test for a covariance of the different individual currents (at the beginning of the experiment due to different pain sensitivity, and at the end of the 16 min equilibration period due to additional individual differences of adaptation during the equilibration period) ANCOVA with the following covariates (continuous predictor) was performed: (i) the current at beginning of the experiment and (ii) the normalized current at the end of the 16 min equilibration period. To assess statistically significant differences between hyperalgesic areas for inter-group comparisons the U-test and for intra-group comparisons the Wilcoxon matched pairs test was used. \( P<0.05 \) were considered to be statistically significant.

Results

Characterization of patients and controls

CRPS patients

A detailed clinical characterization of the CRPS patients can be seen in Table 1. The mean age of the patients was 57.6 ± 2.56 years which was not different compared to the control group (\( P>0.05 \)). Twenty-two patients had CRPS I, three had CRPS II. The mean CRPS-duration was 22.12 ± 4.3 months. Nine of the patients were males and 18 were females. The affected side was the left hand in 16 patients and the right hand in 11 patients. All of the patients reported spontaneous pain. The mean pain on a numeric rating scale (NRS; from 0 to 10) and mean MPQ PRI during the previous 4 weeks was 4.66 ± 0.38/ 21.77 ± 2.40, the mean NRS (0–10) and mean MPQ PRI during the hour previous to the experiment was 3.78 ± 0.44/ 15.30 ± 2.30. Pinprick hyperalgesia was present in 24 of the patients, dynamic mechanical allodynia was present in 21 of the patients. Motor symptoms were present in 23 patients, autonomic disturbances were seen in all of the patients (details see Table 1). The mean pinprick hyperalgesic area of the affected hand was 39.3 ± 6.74% of the total hand surface. The distribution of areas of pinprick hyperalgesia and dynamic-tactile allodynia is depicted in Fig. 1.

Healthy controls

The mean age of the control group (3 males, 11 females, mean age 52.8 ± 3.43 years) was 52.8 ± 3.43 years. None of the controls reported spontaneous pain. Pinprick hyperalgesia or dynamic mechanical allodynia were not present.

Psychophysical measurements

Pain and tactile thresholds

EDTs before stimulation, MDTs and MPTs before and after stimulation are depicted in Table 2. In detail, EDTs were (i) significantly higher in the CRPS affected hand group compared with the CRPS-unaffected hand group (\( P<0.05 \)). For analysis of MDTs and MPTs of the different groups ANOVA with the two factors ‘group’ (levels: CRPS affected, CRPS unaffected, control) and ‘time’ (levels: pre, post) was performed. For MDTs there was (ii) a significant effect of the factor group (\( P=0.005, \) ANOVA) with a higher MDT in ‘CRPS affected’ compared with ‘control’ (\( P=0.004, \) Bonferroni test), there was no significant difference between ‘CRPS unaffected’ and ‘control’ (\( P=0.18, \) Bonferroni test) and ‘CRPS affected’ and ‘CRPS unaffected’ (\( P=0.48, \) Bonferroni test). We also found (iii) a significant effect of the factor time (\( P<0.0001, \) ANOVA) with a higher MDT in the post-condition (\( P<0.0001, \) Bonferroni test). There was no significant interaction of the factors group and time (\( P=0.73, \) ANOVA). Post hoc comparison revealed (iv) a significant difference between the pre- and the post-condition in all three groups (controls \( P=0.010, \) CRPS affected \( P=0.034, \) CRPS unaffected \( P=0.0011, \) Bonferroni test). There was no significant difference between the pre-conditions of the different groups (\( P>0.05 \), Bonferroni test).
Table 1 Demographic data, diagnoses, symptoms and treatment of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Inciting event</th>
<th>NRS/PRI initial</th>
<th>NRS/PRI 1-h-pre</th>
<th>NRS/PRI 4-weeks-pre</th>
<th>Touch</th>
<th>Mechanical hyperalgesia</th>
<th>Alldynia</th>
<th>Cold hyper-sensitivity</th>
<th>Motor symptoms</th>
<th>Autonomic disturbances</th>
<th>Time from onset (months)</th>
<th>Medication</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>Female</td>
<td>CRPS I</td>
<td>Left Distal radius fracture</td>
<td>4/13</td>
<td>2/7</td>
<td>5/17</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>Hair/nails – Skin temp. + oedema</td>
<td>15</td>
<td>Pregabalin</td>
<td>Diabetes, Hypertension</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>Female</td>
<td>CRPS I</td>
<td>Right Shoulder luxation</td>
<td>6/34</td>
<td>3/17</td>
<td>7/33</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>Reddish skin</td>
<td>3</td>
<td>/</td>
<td>Hypertension</td>
</tr>
<tr>
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<td>46</td>
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<td>CRPS I</td>
<td>Left Hand surgery</td>
<td>9/49</td>
<td>6/32</td>
<td>8/36</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dystonia</td>
<td>Oedema red skin</td>
<td>2</td>
<td>Opioid, amitryptil</td>
<td>/</td>
</tr>
<tr>
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<td>CRPS I</td>
<td>Left Metacarpus fracture</td>
<td>8/21</td>
<td>2/6</td>
<td>5/13</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Tremor</td>
<td>White skin oedema</td>
<td>7</td>
<td>Gabapentin</td>
<td>/</td>
</tr>
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<td>CRPS I</td>
<td>Left Minor injury</td>
<td>5/12</td>
<td>4/2</td>
<td>5/11</td>
<td>Hypesthesia</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Paresis</td>
<td>White skin oedema</td>
<td>6</td>
<td>Hypertension</td>
<td></td>
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<td>Left Proximal forearm fracture</td>
<td>9/17</td>
<td>0/0</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>Tremor</td>
<td>Oedema sweating +</td>
<td>7</td>
<td>/</td>
<td>Low back pain</td>
</tr>
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<td>CRPS I</td>
<td>Left Humerus fracture</td>
<td>6/16</td>
<td>5/0</td>
<td>5/8</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>Reddish skin</td>
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<td>Pregabalin</td>
<td>Hypertension, Osteoporosis, Low back pain</td>
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<td>Left Distal radius fracture</td>
<td>8/9</td>
<td>2/6</td>
<td>3/7</td>
<td>Normal</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Paresis</td>
<td>Oedema sweating +</td>
<td>15</td>
<td>/</td>
<td>/</td>
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<td>CRPS I</td>
<td>Left Distal radius fracture + ulna fracture</td>
<td>4/16</td>
<td>5/14</td>
<td>5/17</td>
<td>Normal</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>Reddish skin hair/nails + oedema</td>
<td>3</td>
<td>Opioid calcitonin methylprersolone</td>
<td>/</td>
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<tr>
<td>10</td>
<td>42</td>
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<td>CRPS I</td>
<td>Left Metacarpus fracture</td>
<td>7/33</td>
<td>7/24</td>
<td>7/39</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>Cyanotic skin hair/nails + oedema sweating +</td>
<td>20</td>
<td>NSAID, amitryptil</td>
<td>Low back pain, Hypertension</td>
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<td>CRPS II</td>
<td>Left Surgery for carpal tunnel syndrome</td>
<td>7/34</td>
<td>3/8</td>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>/</td>
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<td>17</td>
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<td>Right Hand surgery</td>
<td>5/12</td>
<td>5/33</td>
<td>5/27</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Paresis</td>
<td>Reddish skin skin temp. + Oedema sweating + Eodema</td>
<td>72</td>
<td>/</td>
<td>Coronary heart disease</td>
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<tr>
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<td>Male</td>
<td>CRPS I</td>
<td>Left Minor injury</td>
<td>9/24</td>
<td>5/27</td>
<td>6/31</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>/</td>
<td></td>
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<td>Male</td>
<td>CRPS I</td>
<td>Left Minor injury</td>
<td>4/26</td>
<td>2/16</td>
<td>2/17</td>
<td>Hypesthesia</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Tremor</td>
<td>Cyanotic skin hair/nails + oedema sweating +</td>
<td>30</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>15</td>
<td>52</td>
<td>Female</td>
<td>CRPS I</td>
<td>Left Hand surgery</td>
<td>4/27</td>
<td>4/25</td>
<td>3/38</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Paresis</td>
<td>White skin hair/nails+ oedema sweating + Reddish skin</td>
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<td>NSAID</td>
<td>/</td>
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<tr>
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<td>0/0</td>
<td>0/0</td>
<td>Normal</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Paresis</td>
<td></td>
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<tr>
<td>17</td>
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<td>6/9</td>
<td>6/13</td>
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<td>+</td>
<td>–</td>
<td>+</td>
<td>Paresis</td>
<td>Reddish skin</td>
<td>28</td>
<td>/</td>
<td>Hypertension</td>
</tr>
<tr>
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<td>37</td>
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<td>5/42</td>
<td>4/24</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>/</td>
<td></td>
<td>24</td>
<td>Paracetamol, opioid, pregabalin</td>
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(continued)
Table 1 Continued

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<tr>
<th>Patient No.</th>
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<th>Gender</th>
<th>Diagnosis</th>
<th>CRPS Inciting event</th>
<th>NRS/PRI initial</th>
<th>NRS/PRI 1-h-pre</th>
<th>NRS/PRI 4-weeks-pre</th>
<th>Touch Mechanical hyperalgesia</th>
<th>Allodynia Cold hyper-sensitivity</th>
<th>Motor symptoms</th>
<th>Autonomic disturbances</th>
<th>Time from onset (months)</th>
<th>Medication</th>
<th>Comorbidity</th>
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<td>19</td>
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<td>9/51</td>
<td>10/28</td>
<td>10/49</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>Paresis Tremor Myoklonus</td>
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<td>/</td>
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<td>20</td>
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<td>4/3</td>
<td>5/26</td>
<td>Normal</td>
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<td>+</td>
<td>Paresis Tremor</td>
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<td>/</td>
<td>Hypertension</td>
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<td>Right Radius and ulna fracture</td>
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<td>4/14</td>
<td>4/12</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>Tremor Cyanotic skin hair/nails + oedema sweating +</td>
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<td>1/3</td>
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<td>+</td>
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<td>36</td>
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<td>73</td>
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<td>+</td>
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<td>Right Distal radius fracture</td>
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<td>Normal</td>
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<td>+</td>
<td>Paresis Cyanotic skin hair/nails+ skin temp.+ oedema sweating +</td>
<td>5</td>
<td>/</td>
<td>NSAID</td>
</tr>
<tr>
<td>26</td>
<td>36</td>
<td>Female</td>
<td>CRPS I</td>
<td>Right Distal radius fracture</td>
<td>5/12</td>
<td>5/12</td>
<td>5/12</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>Paresis Oedema reddish skin</td>
<td>4</td>
<td>/</td>
<td>NSAID</td>
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<tr>
<td>27</td>
<td>42</td>
<td>Male</td>
<td>CRPS I</td>
<td>Left Distal radius fracture</td>
<td>5/18</td>
<td>5/18</td>
<td>5/18</td>
<td>Hypesthesia</td>
<td>+</td>
<td>+</td>
<td>Paresis Oedema reddish skin</td>
<td>4</td>
<td>/</td>
<td>NSAID</td>
</tr>
</tbody>
</table>

NRS = numeric rating scale; PRI = pain rating index of the McGill pain questionnaire; NSAID = non steroidal anti-inflammatory drugs; / = not present.
and no significant difference between the post-conditions of the different groups ($P > 0.05$, Bonferroni test). For MPTs there was (v) a significant effect of the factor group ($P = 0.049$, ANOVA) with a lower MPT in ‘CRPS affected’ compared with ‘control’ ($P = 0.0478$, Bonferroni test), but there was no significant difference between ‘CRPS unaffected’ and ‘control’ ($P = 0.38$, Bonferroni test) and ‘CRPS affected’ and ‘CRPS unaffected’ ($P > 0.05$, Bonferroni test). We also found (vi) a significant effect of the factor time ($P = 0.001$, ANOVA) with a higher MPT in the post-condition ($P = 0.001$, Bonferroni test). There was no significant interaction of the factors group and time ($P = 0.78$, ANOVA).

Post hoc comparison revealed no significant difference between the pre- and the post-condition in all three groups ($P > 0.05$, Bonferroni test). There was also no significant difference between the pre-conditions of the different groups ($P > 0.05$, Bonferroni test) and no significant differences between the post-conditions of the different groups ($P > 0.05$, Bonferroni test). Figure 2 summarizes the corresponding MDTs and MPTs in CRPS patients compared before and after the electrical stimulation.

Pain adaptation

The normalized current during the equilibration period and the pain ratings during the adaptation period are depicted in Fig. 3. Firstly, the normalized current needed to maintain a pain rated NRS=6 was not significantly different between the three groups (i.e. control group, CRPS affected hand group, CRPS unaffected hand group) at the beginning of the experiment ($P = 0.29$, ANOVA). There was a significant increase in current needed to maintain a pain rating of 6 in all three groups together (i.e. control group, CRPS affected hand group, CRPS unaffected hand group) ($P < 0.0001$, ANOVA). Also a significant interaction of the factors group and time was present ($P = 0.039$, ANOVA). However, post hoc comparisons for group or hand effects were not significant ($P > 0.05$, Bonferroni tests). Secondly, during the adaptation period significantly less adaptation was found for the CRPS patients compared with the control group. There was a significant effect of the factor group ($P = 0.013$, ANOVA) with significant less adaptation in CRPS patients compared to controls ($P = 0.013$, Bonferroni test). Interestingly, there was no significant

Table 2 Mechanical detection and pain thresholds

<table>
<thead>
<tr>
<th></th>
<th>EDT pre</th>
<th>EPT pre</th>
<th>MDT pre</th>
<th>MDT post</th>
<th>MPT pre</th>
<th>MPT post</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>1.48 ± 0.08</td>
<td>3.80 ± 0.28</td>
<td>8.14 ± 1.59</td>
<td>13.86 ± 3.07*</td>
<td>310.82 ± 44.70</td>
<td>267.09 ± 43.20</td>
</tr>
<tr>
<td>CRPS Ipsi</td>
<td>1.62 ± 0.13</td>
<td>4.31 ± 0.47</td>
<td>28.04 ± 5.96</td>
<td>47.10 ± 10.43*</td>
<td>213.60 ± 42.93</td>
<td>148.99 ± 33.34</td>
</tr>
<tr>
<td>CRPS contra</td>
<td>1.32 ± 0.04</td>
<td>4.16 ± 0.37</td>
<td>15.58 ± 3.09</td>
<td>40.29 ± 11.98*</td>
<td>278.11 ± 47.67</td>
<td>221.84 ± 46.08</td>
</tr>
</tbody>
</table>

* $P < 0.05$, post hoc Bonferroni test. Means ± SEM.
difference between the affected and the unaffected hand in CRPS patients: there was no significant effect of the factor side ($P = 0.45$, ANOVA), with no significant differences between the affected and the unaffected hand of patients or left and right hand of controls ($P > 0.05$, Bonferroni test). The effect of the factor time was significant ($P < 0.0001$, ANOVA), with significantly lower pain ratings in the course of stimulation ($P < 0.05$, Bonferroni test). There was a significant interaction of the factors ‘group’ and ‘time’ ($P = 0.007$, ANOVA). Post hoc Bonferroni test did not reveal significantly different pain ratings between the two groups at single time points ($P > 0.05$, Bonferroni test).

To test for a covariance of the different individual currents (at the beginning of the experiment due to different pain sensitivity, and at the end of the 16 min equilibration period due to additional individual differences of adaptation during the equilibration period) ANCOVA with the following covariates (continuous predictor) were performed: (i) the current at beginning of the experiment and (ii) the normalized current at the end of the 16 min equilibration period. A significant difference was found for the comparison of pain adaptation in CRPS patients versus controls with both covariates [(i) current at beginning of the experiment $P = 0.0062$, ANCOVA; (ii) normalized current at the end of the 16 min equilibration period $P = 0.018$, ANCOVA]. The covariate (i) current at beginning of the experiment had no significant effect ($P = 0.25$, ANCOVA). The covariate (ii) normalized current at the end of the 16 min equilibration period had a significant effect ($P < 0.0001$, ANCOVA) on the following course of pain adaptation. Those subjects with a high adaptation (upregulation...
of current to maintain a stable level of pain) in the equilibration period had also high adaptation in the following course of adaptation. The initial current needed to induce the targeted pain rating however has no effect of the adaptation course.

For analysis of pain adaptation of the 24 patients with CRPS I alone a subgroup analysis was performed. Thus, the three patients with CRPS II were excluded from the analysis. Comparing this subgroup to controls there was also a significant effect of the factor ‘group’ with significantly decreased adaptation in CRPS I patients (P = 0.043, ANOVA).

Hyperalgesic areas
The area of electrically induced pinprick hyperalgesia as measured 10 min post-stimulation is presented in Fig. 3C. Areas of pinprick hyperalgesia patients on the affected hand were present 10 min after stimulation in 64% of controls (n = 16 of 25 measurements), in 67% (n = 18 of 27) of CRPS patients on the affected hand and in 70% (n = 19 of 27) of CRPS patients on the unaffected hand. The area of pinprick hyperalgesia in individuals displaying hyperalgesia was significantly greater in CRPS patients on the affected hand compared with controls (P < 0.05; U-test) and to the unaffected hand (P < 0.05; Wilcoxon matched pairs test). The area was 8.03 ± 1.18 cm² for the control group, 12.72 ± 1.36 cm² for the CRPS affected hand group and 7.80 ± 1.44 cm² for the CRPS unaffected hand group.

Laser Doppler imaging
Axon-reflex flare
The area of the axon reflex flare did not differ between the three groups. In the CRPS affected hand group it was 2.2 ± 0.4 cm², in the CRPS unaffected hand group it was 2.6 ± 0.5 cm² and in the control group it was 2.1 ± 0.4 cm² (P > 0.05 for all comparisons, U-test and Wilcoxon matched pairs test, respectively).

Correlation analysis
The z-scores of (i) adaptation and (ii) hyperalgesic area were tested for correlation among each other, with clinical characteristics of the CRPS and with the experimentally obtained data. No significant correlation (P < 0.05) of these both parameters was found (i) among each other ([adaptation and hyperalgesic area affected hand (HAA)] r = 0.18, unaffected hand r = 0.08); for (ii) the CRPS duration [adaptation affected hand (AA) r = −0.28, HAA r = −0.27, adaptation unaffected hand (AU) r = −0.12, hyperalgesic area unaffected hand (HAU) r = 0.08]; (iii) pain intensity obtained by the numeric rating scale regarding: (a) spontaneous pain for the time 1 h previous to the experiment and (AA r = 0.05, HAA r = −0.04, AU r = −0.30, HAU r = 0.04); (b) spontaneous pain averaged over the last 4 weeks NRS (AA r = 0.21, HAA r = 0.18, AU r = −0.14, HAU r = −0.02); (iv) pain intensity obtained by the PRI of the German counterpart of the MPQ regarding: (a) spontaneous pain for the time 1 h previous to the experiment (AA r = −0.08, HAA r = −0.23, AU r = −0.12, HAU r = −0.11) and (b) spontaneous pain averaged over the last 4 weeks (AA r = 0.04, HAA r = −0.11, AU r = −0.20, HAU r = −0.14); (v) the sum score of motor symptoms (AA r = −0.16, HAA r = −0.17, AU r = −0.31, HAU r = −0.2); (vi) the sum score of autonomic disturbances (AA r = −0.23, HAA r = −0.12, AU r = −0.03, HAU r = −0.24); (vii) medications used at the day of the experiment: (a) tricyclic antidepressants (AA r = 0.29, HAA r = −0.19, AU r = 0.19, HAU r = 0.01), (b) opioids (AA r = 0.24, HAA r = −0.3, AU r = 0.02, HAU r = −0.25), (c) gabapentin and pregabaline (AA r = −0.17, HAA r = 0.07, AU r = −0.35, HAU r = −0.04), (d) NSAID (AA r = 0.06, HAA r = −0.06, AU r = −0.16, HAU r = 0.07); (viii) age (AA r = −0.10, HAA r = 0.21, AU r = 0.13, HAU r = 0.01).

Significant positive correlation was found for (i) the z-score of adaptation of the affected hand and the z-score of adaptation of the unaffected hand (r = 0.56; P = 0.02, Bonferroni corrected); and (ii) the z-score of hyperalgesic area of the affected hand and the z-score of hyperalgesic area of the unaffected hand (r = 0.71; P = 0.001, Bonferroni corrected). The significant correlations are depicted in Fig. 4.

Discussion
In the present study, we show that CRPS patients display differential activity in endogenous pain modulatory systems.
The major findings are (i) that adaptation to repetitive painful high current density electrical stimuli is decreased in CRPS patients on both the affected and the unaffected hand compared to healthy controls and (ii) that the resulting hyperalgesic areas are significantly enhanced in CRPS patients on the affected side. These changes are not correlated to disease duration, pain intensity, the degree of pre-existing hyperalgesic areas, the presence of motor symptoms or autonomic disturbances nor any other CRPS symptom.

However, time course of adaptation and extent of experimen-tally induced hyperalgesia on the affected hand correlated significantly with those on the contralateral unaffected hand. Two major assertions can be considered as mechanisms underlying these find-ings: (i) the endogenous pain modulatory system in CRPS patients has to deal with increased nociceptive input from the periphery and therefore its residual inhibitory capacity is decreased com-pared with healthy subjects; or (ii) the shift from net inhibition towards net facilitation in endogenous pain modulating systems is not a result of CRPS but a risk factor for its appearance (Edwards, 2005). For the first hypothesis, we would expect the changes to be correlated with individual disease characteristics like duration or painfulness. However, such a correlation was non-existent in the present study. This contrasts cortical reorganization phenomena which result from nociceptive input and were shown to correlate with pain intensity and pinprick hyperalgesia (Maihofner et al., 2003, 2004). Nevertheless, we cannot exclude that the presence of neuropathic pain altered central processing of nociceptive stimuli, resulting in similar changes in affected and unaffected regions, for example by alteration of diffuse noxious inhibitory control system, without a correlation with individual disease characteristics. Especially pre-existing central sensitization in CRPS patients may have modified CNS processing and endogen-ous modulation of the painful stimuli. For example, LTD and LTP is induced by repetitive electrical low-frequency stimulation in ani-mals (Sandkuhler et al., 1997). Such changes in synaptic strength are suggested to be involved in both the adaptation to repetitive electrical stimuli (homotopic LTD) and the occurrence of secondary pinprick hyperalgesia (heterotopic LTP) (Klein et al., 2004, 2006), although definitive evidence for contribution of these cellular mechanisms to the observed effects in humans is lacking. LTD and LTP mechanisms could be altered in the patient group due to previous continuous nociceptive input from the CRPS affected hand. However, in the employed pain model activation of descending naloxone-sensitive and naloxone-insensitive pain modula-tory systems is more likely to contribute to the observed effects of adaptation and hyperalgesia (Koppert et al., 2005). There is pro-found evidence for pronounced and sustained alteration in the activity of descending controls under the conditions of pathol-ogical pain due to tissue or peripheral nerve damage in the literature (Baranauskas and Nistri, 1998; Danziger et al., 1999; Woolf and Mannion, 1999; Millan, 2002). Long term noxious stimulation was found to be associated with a progressive reinforcement in mechanisms of descending inhibition, reflecting the recruitment of descending pathways originating in the RVM and noradrenergic nuclei (Basbaum and Fields, 1984; Millan, 2002). On the other hand, adaptive changes in descending pain control during chronic pain can be also of unfavourable character (Millan, 2002). There is now evidence that persistent activation of descending facilitation amplifies neuronal sensitization in the dorsal horn and contributes to chronic painful states (Urban et al., 1996; Mansikka and Pertovaara, 1997; Wiertelak et al., 1997; Pertovaara, 1998; Ossipov et al., 2000; Porreca et al., 2001). Subcortical regions including the thalamus could also be involved in pain modulatory processes. Single neurons with whole body representation have been shown in the lateral ventromedial thalamic nucleus. These neurons relay widespread nociceptive inputs from the medullary reticular formation to the dorsolateral frontal cortex (Monconduit et al., 1999; Monconduit and Villanueva, 2005).

The second hypothesis implies that there is a pre-existing in-dividual difference in the activity in pain modulatory networks. This assumption is supported by the significant correlation of the amount of adaptation and the extent of experimentally induced hyperalgesia on the affected hand with those on the contralateral unaffected hand. However, if differential activity in pain modulatory systems is present in CRPS patients one may expect that the individual degree of activity in these pain inhibitory and facilitatory systems correlates with individual disease characteristics, e.g. pain intensity or the area of CRPS-related hyperalgesia. However, we did not find such a correlation in our data. Nevertheless, support-ive evidence for this hypothesis, i.e. that pre-existing individual differences in endogenous pain modulation are risk factors for the development of chronic pain, can be found in the literature (Edwards, 2005). However, no study was so far performed in CRPS patients investigating this topic. Basically, endogenous pain modulation in humans may be tested by the (i) wind up pheno-non, thus the application of repeated painful stimuli and consecu-tive measurement of the increase of pain which reflects a pre-stage to central sensitization and is mediated by NMDA recep-tors (Woolf and Thompson, 1991; Vierck et al., 1997; Edwards, 2005), (ii) by parallel application of two noxious stimuli and mea-surement of the resulting inhibition (diffuse noxious inhibitory con-trol, DNIC) (Willer et al., 1984) or by (iii) repetitive application of noxious stimuli and measurement of the resulting adaptation over the time course (Koppert et al., 2001, 2005). Interestingly, a prospective study on the development of CRPS after knee arthro-plasty found correlation between high preoperative pain and postoperative development of CRPS symptoms (Harden et al., 2003). Inter-individual and interracial differences in pain sensitivity are well documented in animals and human (Mogil et al., 1999a, b, 2005; Edwards et al., 2003; Rolke et al., 2006). Neurophysiological correlates for these differences in psychophysical pain responses can be found on all levels of the neuraxis (Coghill et al., 2003; Mogil et al., 2005). These differences can be inherited (Lotsch and Geisslinger, 2007) or acquired by envi-ronmental factors or psychosocial processes (Edwards et al., 1985; MacGregor et al., 1997; Taddio et al., 1997, 2002; Gracely et al., 2004; Rollman et al., 2004). However, a genetic factor influencing pain modulatory systems per se is not known yet. To further prove the hypothesis of differential endogenous pain modulation as a risk factor for CRPS development, prospective studies sampling psychophysical profiles of healthy individuals and follow up inves-tigations for development of CRPS would be needed. Additionally, there may be also a combination of both, (i) inter-individual dif-fferences in the activity of descending modulation and (ii) CRPS...
induced changes in the relation of descending inhibition or facilitation.

Another factor potentially contributing to a differential pain modulation in CRPS patients is altered autonomic influence on descending systems. Interactions between sympathetic and parasympathetic centres and descending pain modulation has been reported (Millan, 2002). However, there was no correlation between autonomic symptoms and parameters resembling pro- and anti-nociceptive systems in the present study. Finally, an interaction of the medication present in the CRPS group interfering with pain modulatory systems cannot be excluded. However, one would expect increased adaptation and reduced hyperalgesia rather than the opposite by pain medication. Furthermore, no significant correlation was found between one of the medications used by the patients (NSAIDs, opioids, adjuvant analgesics) and the adaptation curves. A contribution of peripheral mechanisms underlying the observed differences cannot be completely ruled out. However, this seems unlikely considering the evidence for centrally mediated mechanisms underlying adaptation (Klein et al., 2004; Koppert et al., 2005) and secondary mechanical hyperalgesia in our experimental paradigm (Klede et al., 2003; Klein et al., 2004; Koppert et al., 2005). In a subgroup analysis of CRPS I patients only the adaptation behaviour was also significantly different. Thus, an explanation of the observed differences between CRPS patients and controls with the presence of a damaged peripheral nerve in those three patients with CRPS II is not justified, particularly due to the fact that the stimulation was performed on the dorsum of the hand and not in median nerve innervated skin.

Further findings of the present study were a significant shift of the tactile detection threshold induced by the electrical stimulation in both, patients and controls. Thus, hypoesthesia occurred. This phenomenon was recently described (De Col and Maihofner, 2008) and could be a result of prompt plastic CNS changes due to c-fibre input. Also, we found a significant difference in the tactile detection threshold between the affected hand of the patients and controls. This finding was expected as hypoesthesia was clinically present in a majority of our and of other CRPS patients.

In conclusion, adaptation to repetitive painful high current density electrical stimuli was found to be decreased in CRPS patients on both the affected and the unaffected hand compared with healthy controls. The resulting hyperalgesic areas were significantly enhanced in CRPS patients on the affected side. These changes were not correlated to individual disease symptoms. Therefore, we hypothesize that differential activity in endogenous pain modulating systems could be not only a result of CRPS but may be a risk factor for its development. To evaluate the underlying mechanisms in pain modulation, imaging studies focussing on the brainstem (Tracey and Iannetti, 2006) and, increasingly feasible, the spinal cord (Brooks and Tracey, 2005) are warranted.

Acknowledgements
We thank Conny Hofmann for excellent technical assistance.


