Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome

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Summary

Pain sensitivity was assessed in 11 patients (age 60 ± 10 years) with ‘primary’ restless leg syndrome (RLS) (disease duration 18 ± 15 years) and 11 age- and gender-matched healthy control subjects. Stimulus-response functions for pricking pain were obtained with seven calibrated punctate mechanical stimulators activating Aδ-high threshold mechano-nociceptors. Stimuli at the foot were significantly more painful than at the hand in both patients and healthy control subjects both in the morning and evening. Generally, pin-prick pain ratings in RLS patients were significantly elevated, by a factor of 5.3 in the upper limb and by a factor of 6.4 in the lower limb indicating a significant generalized static hyperalgesia more pronounced in the lower limb. In contrast, pain to light touch (allodynia = dynamic mechanical hyperalgesia) as tested by a battery of three gentle tactile stimuli was never reported. Acute single-dose dopaminergic treatment with 100 mg levodopa + 25 mg benserazide, 90 min prior to the evening measurements, largely resolved patients’ RLS symptoms, but had no effect on pin-prick pain. Static hyperalgesia to pin-prick, however, was significantly reversed (median reduction ~74%) by long-term individually tailored dopaminergic treatment. Our study shows that patients with RLS exhibit a profound static mechanical hyperalgesia to pin-prick stimuli, but no dynamic mechanical hyperalgesia (allodynia). This type of hyperalgesia is probably mediated by central sensitization to Aδ-fibre high-threshold mechanoreceptor input, a hallmark sign of the hyperalgesia type of neuropathic pain. The reduction of hyperalgesia in RLS patients by long-term dopaminergic treatment suggests that the pathophysiology of RLS includes disturbed supraspinal pain modulation involving the basal ganglia and/or descending dopaminergic pathways.

Keywords: restless legs syndrome; pathophysiology; pain; nociceptive processing

Abbreviations: ANCOVA = analysis of covariance; IRLS = International RLS study Group severity scale; IRLSSG = International RLS Study Group; LSD = least squares differences; NMDA = N-methyl-D-aspartate; PLM = periodic leg movements; PLMS = periodic leg movements in sleep; PLMW = periodic leg movements during wakefulness; REM = rapid eye movement; RLS = restless legs syndrome

Introduction

Restless legs syndrome (RLS) is characterized by a desire to move the limbs, usually associated with unpleasant sensations in the lower extremities, less often in the arms. RLS symptoms are worse or exclusively present while being at rest in the evening or night time with at least partial and temporary relief by activity (Walters et al., 1995; Allen et al., 2003). As a consequence, many RLS patients suffer from severe sleep disturbances with impaired quality of life (Walters et al. 2003). RLS is frequently associated with end-stage renal disease (Winkelman et al., 1996; Collado-Seidel et al., 1998), pregnancy (Goodman et al., 1988) or iron deficiency (Roger et al., 1991; O’Keeffe et al., 1994) and disappears with resolution of the precipitating condition (Yasuda et al., 1986; McParland and Pearce, 1990; O’Keeffe
Peripheral neuropathies have been suggested to be associated with RLS, but supporting data are limited. In several case reports, RLS has been linked with subclinical sensory neuropathy (Polydefkis et al., 2000), axonal neuropathy (Iannaccone et al., 1995), cryoglobulinamic neuropathy (Gemignani et al., 1997), amyloid neuropathy (Salvi et al., 1990) and Charcot–Marie–Tooth neuropathy type 2 (Gemignani et al., 1999). However, RLS has been reported in only 5.2% of patients with polyneuropathy (Rutkove et al., 2000), which does not exceed the prevalence in the general population (Rothdach et al., 2000).

Though scientific interest in RLS expanded rapidly during the last few years, little is known about the origin and pathophysiology of this disorder. Medication responses to dopaminergic or opioidergic treatment (Chesson et al., 1999) suggest that RLS is a disorder of respective central nervous transmitter systems. Flexor reflex studies showed an increased spinal cord excitability during sleep in RLS patients, indicating that altered signal processing in the spinal cord may play a major role in the pathophysiology of RLS (Bara-Jimenez et al., 2000). Dysfunction in other CNS structures, in particular cortical or subcortical areas, has also been suggested (Tergau et al., 1999). Overall, the pathophysiology and its CNS location involved in RLS are uncertain.

Disagreeable and sometimes painful sensory symptoms are a characteristic feature of RLS. We sought, therefore, to elucidate the question whether pain sensitivity and nociceptive processing are altered in these patients. The enhanced flexor reflex excitability suggests that the sensory symptoms in RLS may be related to central sensitization in the spinal cord (Woolf, 1983; Grönnroos and Pertovaara, 1993). This central sensitization leads to enhanced responses of spinal nociceptive neurons to mechanical, but not heat stimuli (Dougherty et al., 1998; Pertovaara, 1998; Simone et al., 1991). The perceptual correlate of central sensitization is called neurogenic hyperalgesia (LaMotte et al., 1991; Treede and Magerl, 2000). Neurogenic hyperalgesia can be specifically assessed by two sets of mechanical probes, one that activates tactile receptors by moving gentle stimuli for testing dynamic mechanical hyperalgesia (allodynia), and one that activates mechano-nociceptors by punctate mechanical stimuli for testing static mechanical hyperalgesia (Greenspan and McGillis, 1991; Chan et al., 1992; Koltzenburg et al., 1992; Ochoa and Yarnitsky, 1993; Ziegler et al., 1999; Magerl et al., 2001; Andrew and Craig, 2002). Using these methods, we report here that RLS patients exhibit a pronounced static mechanical hyperalgesia similar to patients with neuropathic pain of various origins (Fields et al., 1998; Baumgärtner et al., 2002; Jensen and Baron, 2003) but, in contrast to neuropathic pain patients, none of the RLS patients exhibited any signs of dynamic mechanical hyperalgesia (allodynia).

### Methods

#### Patients and control subjects

We investigated 11 untreated patients (10 female and one male, mean age 60 ± 10 years, range 37–73 years) with moderate to very severe ‘primary’ RLS according to the diagnostic criteria of the International RLS Study Group (IRLSSG) (Walters, 1995; Allen et al., 2003) with a disease duration of 18 ± 15 years (range 1–40 years) and 11 age- and gender-matched healthy control subjects (10 female and one male; mean age 60 ± 11 years, range 41–82 years). Patients were consecutively enrolled if they suffered from at least moderate RLS and had no RLS-specific or other centrally active medication. Selection of the patients was based on the inclusion

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Duration of RLS (years)</th>
<th>Family history</th>
<th>RLS therapy in patients available for follow-up</th>
<th>NCV</th>
<th>EMG</th>
<th>SL (min)</th>
<th>TST (min)</th>
<th>SE</th>
<th>PLM index</th>
<th>PLMS arousal index</th>
<th>Improvement with 100 mg levodopa</th>
<th>Overall ‘RLS symptoms’ (before→after)</th>
<th>‘Urge to move’ (before→after)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>F</td>
<td>1</td>
<td>–</td>
<td>200 mg levodopa</td>
<td>Normal</td>
<td>nt</td>
<td>12</td>
<td>416</td>
<td>85</td>
<td>26</td>
<td>10</td>
<td>nt</td>
<td>94→14</td>
<td>85→16</td>
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<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>30</td>
<td>+</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
<td>53</td>
<td>223</td>
<td>47</td>
<td>57</td>
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<td>98→27</td>
<td>94→32</td>
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<td>3</td>
<td>63</td>
<td>F</td>
<td>30</td>
<td>+</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
<td>29</td>
<td>285</td>
<td>61</td>
<td>59</td>
<td>17</td>
<td>nt</td>
<td>nt</td>
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<td>59</td>
<td>F</td>
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<td>–</td>
<td></td>
<td>Normal</td>
<td>nt</td>
<td>70</td>
<td>295</td>
<td>64</td>
<td>27</td>
<td>20</td>
<td>nt</td>
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<td>57</td>
<td>F</td>
<td>20</td>
<td>–</td>
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<td>nt</td>
<td>131</td>
<td>248</td>
<td>52</td>
<td>58</td>
<td>6</td>
<td>nt</td>
<td>92→54</td>
<td>91→52</td>
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<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>2</td>
<td>–</td>
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<td>Normal</td>
<td>Normal</td>
<td>34</td>
<td>375</td>
<td>82</td>
<td>67</td>
<td>28</td>
<td>37→1</td>
<td>37→2</td>
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<td>70</td>
<td>F</td>
<td>10</td>
<td>–</td>
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<td>nt</td>
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<td>176</td>
<td>62</td>
<td>33</td>
<td>18</td>
<td>90→2</td>
<td>96→2</td>
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<td>73</td>
<td>F</td>
<td>10</td>
<td>–</td>
<td>1.5 mg cabergoline</td>
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<td>Normal</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>26</td>
<td>nt</td>
<td>nt</td>
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</tr>
<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>3</td>
<td>+</td>
<td></td>
<td>Normal</td>
<td>nt</td>
<td>13</td>
<td>400</td>
<td>87</td>
<td>6</td>
<td>1</td>
<td>82→46</td>
<td>83→43</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>M</td>
<td>40</td>
<td>+</td>
<td></td>
<td>Normal</td>
<td>nt</td>
<td>34</td>
<td>310</td>
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<td>3</td>
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<td>61→21</td>
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</tr>
<tr>
<td>11</td>
<td>56</td>
<td>F</td>
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<td>Normal</td>
<td>26</td>
<td>355</td>
<td>73</td>
<td>33</td>
<td>6</td>
<td>72→2</td>
<td>68→3</td>
<td></td>
</tr>
</tbody>
</table>

NCV = nerve conduction velocities; EMG = electromyography; SL = sleep latency; TST = total sleep time; SE = sleep efficiency; PLM index = periodic leg movements per hour time in bed; PLMS = periodic leg movements per hour total sleep time; PLMS arousal index = PLMS associated arousals per hour total sleep time; F = female; M = male; nt = not tested.
criterion of primary RLS and the absence of peripheral neuropathy or other relevant comorbidity (see below).

RLS diagnosis was made by an experienced examiner (K.S.-K.) and the severity ratings were performed according to the 10-item IRLSSG severity scale (IRLS; 1–10 points, ‘mild’; 11–20, ‘moderate’; 21–30, ‘severe’; 31–40, ‘very severe’) (International Restless Legs Syndrome Study Group, 2003). This scale reflects both subjective assessment of the primary features of RLS, intensity and frequency of symptoms and associated sleep disorders, as well as the impact of symptoms on the patients’ mood and daily functioning. The mean IRLSSG severity scale score was 29.2 ± 5.3.

Six patients suffered from early-onset RLS which is characterized by a symptom onset before age 45 years, slow progression, and high familial aggregation (Allen and Earley, 2000). In all patients only the legs (both sides), but not the arms were affected by sensory and motor symptoms of RLS. Sensory RLS symptoms were described as follows: ‘discomfort’ (n = 11), ‘tension’ (n = 7), ‘crawling’ (n = 7), ‘painful’ (patients 4, 5, 6 and 8). None of the patients exhibited relevant comorbidity, such as iron deficiency, diabetes, vitamin B₁₂ deficiency, uraemia or alcohol abuse. Neurological examination was unremarkable in all participants. In particular, there was no loss of reflexes, sensation to pin-prick, temperature and vibration in distal limbs. Four patients reported a positive family history. In RLS patients, motor nerve conduction velocity of the deep peroneal or tibial nerves and sensory nerve conduction velocity of the sural nerve were normal with normal amplitudes. Likewise electromyography of lower limb muscles revealed no abnormalities. All patients underwent a one-night cardio-respiratory polysomnography which was analysed using standard criteria (Rechtschaffen and Kales, 1968; Atlas Task Force of the American Sleep Disorders Association, 1992, 1997; Pollmächer and Schulz, 1993). In all patients, polysomnography revealed a disturbed sleep profile with reduced total sleep time leading to reduced sleep efficiency. In addition, the microstructure of sleep was frequently fragmented by periodic leg movements (PLM), which were often associated with arousals (PLMS arousals, see Table 1). The study was performed in accordance with the Declaration of Helsinki and was approved by the Philipps University, Marburg ethics committee. Written informed consent was given by all participants.

Sensory testing
To test for the presence of static mechanical hyperalgesia (Ziegler et al., 1999; Baumgärtner et al., 2002), stimulus-response functions for pin-prick pain were obtained with a series of seven punctate mechanical stimulators (φ = 0.2 mm; force, 8–512 mN). These stimuli activate Aδ-high threshold mechano-nociceptors and a specific nociceptive pathway in the superficial spinal cord (Greenspan and McGillis, 1991; Slugg et al., 2000; Andrew and Craig, 2002). Following each stimulus, the patient was asked to rate the magnitude of pain on a verbal numerical rating scale (0 = not painful, 100 = maximal pain imaginable). Pain to light touch (dynamic mechanical hyperalgesia = allodynia) was tested by light stroking with a cotton wisp (3 mN), a Q-tip fixed to an elastic strip (100 mN), and a soft make-up brush (400 mN). In case the stroking stimuli were perceived as painful, patients were asked to use the same numerical rating scale rating (see above). This quantitative sensory testing was performed in the evening (20.00 to 22.00 hours) and the following morning (08.00 to 10.00 hours) in both hand (spinal segments C6 and C7) and foot dorsums (spinal segments L5 and S1). At every test site, the different pin-prick intensities and light touch modalities were applied five times in balanced order.

Levodopa administration and long-term dopaminergic therapy
In RLS patients, sensory testing was repeated in the evening of the second day, 90 min after a single dose of levodopa (100 mg plus 25 mg benserazide) and in the following morning. None of the patients had received any dopaminergic treatment before. Levodopa is known to reach maximum blood levels ~1 h after drug intake and has an expected duration of action of about 4–6 h in RLS patients. Subsequently dopaminergic treatment was initiated and tailored to the individual patient resulting in a complete or substantial relief of RLS symptoms, including sleep disturbances. Pain sensitivity was reinvestigated in those patients available for follow-up testing (six out of 11 patients). The mean follow-up period was 353 ± 114 days (range 170–495 days). At this time point, two patients were sufficiently treated with levodopa (150 and 200 mg) and four with the D2-receptor agonist cabergoline (1–2 mg) given as a single evening dose.

Data analysis
Pin ratings were transformed into decadic logarithms to achieve secondary normal distribution of rating data as suggested by correlation of mean and variances (Barlett, 1947). To avoid loss of zero rating values, a small constant (0.1) was added to each rating before transformation (Magerl et al., 1998). As there were no systematic left/right differences in pain ratings [analysis of covariance (ANCOVA): \( F(1,303) = 0.02; P = 0.89 \)], data from both sides of the body were combined. Pain ratings to light touch and to punctate mechanical stimuli were analysed by a mixed model ANCOVA (repeated measures factors: foot versus hand, evening versus morning; between groups factor: RLS patients versus controls; covariate: stimulus intensity). Group differences were tested by post hoc least squares differences (LSD) tests. Throughout the manuscript, data are presented as mean ± SEM. P-values <0.05 were considered significant.

Results
Pin-prick pain
Figure 1 shows an example of a 50-year-old female patient, who suffered from RLS for 2 years. Her sleep profile (Fig. 1A) revealed a delayed sleep onset latency of 34 min and a moderately reduced total sleep time (375 min) leading to a reduced sleep efficiency. Her disturbed sleep profile revealed periodic leg movements during wakefulness (PLMW) and during sleep (PLMS) about once per minute, the latter leading to frequent arousal reactions. As a consequence, both deep sleep and REM (rapid eye movement) sleep stages were markedly impaired. Sensory testing with punctate mechanical stimulators revealed a stimulus-response function of pin-prick pain that was linear in double logarithmic coordinates (i.e. a power function; Fig. 1B). The highly significant correlation between stimulus force and pain estimate (\( r = 0.83, P < 0.001 \)) indicated that the patient was able to perform the psychophysical task of discriminating different stimulus
intensities of mechanically induced pain. Comparison with age-matched control subjects revealed a pronounced static mechanical hyperalgesia (pain ratings were outside the 95% confidence interval of the control group).

Analysis of group data (Fig. 2) by ANCOVA revealed that the magnitude of pain ratings depended on the stimulus force ($P < 0.001$; Table 2), and stimulus-response functions of similar shape were seen in patients and control subjects. Stimulus forces were discriminated equally well by patients (average $r = 0.93$, range 0.83–0.99) and by control subjects (average $r = 0.96$, range 0.90–0.99). The most prominent finding was dramatically increased pain ratings in RLS patients at all stimulus intensities ($P < 0.001$). The stimulus-response function in RLS patients was shifted in parallel towards higher pain ratings in both hands and feet, resulting in an average increase in pain rating by a factor of 5.8. This finding demonstrates the presence of profound static mechanical hyperalgesia in RLS patients. In both RLS patients and control subjects, pin-prick pain was significantly more intense in the feet than in the hands ($+33\%$; $P < 0.001$), and pain ratings were marginally higher in the early morning than in the evening ($P = 0.077$). There was also a trend towards

Table 2 Analysis of covariance of pain ratings to pin-prick stimuli

<table>
<thead>
<tr>
<th>Factor</th>
<th>Degrees of freedom (effect, error)</th>
<th>$F$-value</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariate: stimulus force</td>
<td>4, 302*</td>
<td>98.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1: patients versus control subjects</td>
<td>1, 305</td>
<td>279.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2: hands versus feet</td>
<td>1, 305</td>
<td>51.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3: evening versus morning</td>
<td>1, 305</td>
<td>3.1</td>
<td>0.077</td>
</tr>
<tr>
<td>1 $\times$ 2 interaction</td>
<td>1, 305</td>
<td>3.8</td>
<td>0.054</td>
</tr>
<tr>
<td>1 $\times$ 3 interaction</td>
<td>1, 305</td>
<td>1.5</td>
<td>0.23</td>
</tr>
<tr>
<td>2 $\times$ 3 interaction</td>
<td>1, 305</td>
<td>0.0</td>
<td>0.96</td>
</tr>
<tr>
<td>1 $\times$ 2 $\times$ 3 interaction</td>
<td>1, 305</td>
<td>7.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Calculated as multivariate ANCOVA (MANCOVA and Rao’s $R$ replacing $F$-value).
stronger hyperalgesia in the feet than in the hands (6.3±3 versus 5.4±3; two-way group × test site interaction, P = 0.054). At a closer look, exaggerated hyperalgesia in the feet of patients was only seen at evening (54% more pain in feet than in hand dorsums compared with only 14% in control subjects), but not at morning assessments (three-way group × test site × test time interaction, P < 0.01). Notably, dynamic mechanical hyperalgesia (allodynia), as assessed by moving gentle tactile stimuli across the skin, was never observed.

Influence of acute and long-term dopaminergic treatment

Dopaminergic substances are a well-accepted treatment to improve RLS symptoms almost instantly, but their effects on the perception of pain in RLS patients are not known. Thus, the impact of dopaminergic treatment on pain sensitivity was tested after initiation of dopaminergic treatment (Post) which subjectively relieved RLS symptoms, all patients exhibited the same degree of static mechanical hyperalgesia as on the day before treatment onset (Pre). Long-term dopaminergic treatment led to a partial reversal of hyperalgesia in those patients available for follow-up testing 12 months later (F-up). Values are mean ± SEM. NRS = numerical rating scale.

quantitative levodopa test (unpublished methodology). ‘RLS symptoms in general’ and the ‘urge to move’ (as measured on a visual analogue scale ranging from 0 = no symptoms to 100 = very severe symptoms) significantly improved 1–2 h after levodopa intake (75 ± 8% and 78 ± 8% relief, respectively; n = 8, P < 0.001), showing a high degree of correlation (r = 0.93, P < 0.001). In contrast, pain sensitivity was not changed at all [ANCOVA: F(1,152) = 1.18; P = 0.28; changes <5%; see Fig. 3]. The absence of improvement in pain sensitivity was similarly observed in both hands and feet [ANCOVA: F(1,152) = 0.61; P = 0.43]. Testing on the following morning revealed similar results (evening and morning assessments, ANCOVA: F(1,166) = 0.21; P = 0.65).

Twelve months later, six out of 11 patients were reinvestigated under stable dopaminergic long-term treatment. In these patients the treatment effect was objectively documented as a decrease of RLS severity as assessed on the IRLS from 27.5 ± 6.3 points at baseline (= severe RLS, n = 6) to 10.2 ± 6.7 points at follow-up (= mild RLS; P < 0.005). A substantial reduction of pin-prick pain was found in all reassessed patients [ANCOVA: F(1,152) = 173.3; P < 0.001; Fig. 3]. As in the whole group of patients, this subgroup exhibited <1% change of pain ratings after acute treatment (P = 0.90, LSD). At 12 months, however, pin-prick pain was reduced by 74% (median value; P < 0.001, LSD), with a significantly more pronounced pain reduction in the foot than in the hand [ANCOVA: F(1,152) = 12.0, P < 0.001]. Single-subject analysis (Fig. 4) confirmed that all patients tested at follow-up (n = 6) displayed statistically significant pain relief.
To identify possible predictors of treatment efficacy, correlations between several signs of RLS pathology and the degree of pain reduction as measured by pin-prick pain ratings at 12-month follow-up were determined. Interestingly, pain relief was independent of the number of periodic leg movement (PLM, \( r = 0.03 \)), but was correlated to other specific sleep parameters determined before initiation of therapy, namely to total sleep time \( (r = -0.81, P < 0.05) \) and number of PLM arousals \( (r = 0.70, P < 0.12) \). These factors together explained 83% of the variance in pain relief data. Thus, impaired initial sleep quality was associated with successful reduction in static mechanical hyperalgesia by dopaminergic therapy.

**Discussion**

This study shows for the first time that patients with RLS exhibit a profound static mechanical hyperalgesia to punctate stimuli, but not a dynamic mechanical hyperalgesia to gentle stroking with light tactile stimuli (allodynia). Thus according to present concepts of pain mechanisms, RLS may be a pain syndrome in addition to being a motor syndrome and a sleep disorder. Pain as a symptom in RLS is severely under-appreciated: a keyword search in PUBMED on the relationship of pain and RLS returned zero publications. In parallel to RLS symptoms, hyperalgesia was significantly more pronounced in the feet than in the hands and tended to be more prominent in the evening than in the morning. The presence of hyperalgesia in the hands, however, contrasted with the absence of RLS symptoms in the upper limbs. Although RLS symptoms responded promptly to single-dose treatment with L-dopa, hyperalgesia was only resolved upon long-term dopaminergic treatment. Our data provide the first evidence that central sensitization of the nociceptive system is a characteristic finding in RLS. The loose correlation of pain and other RLS symptoms in time and in body topography suggests that the relationship between the two may be indirect.

**Central sensitization in RLS**

Mechanical hyperalgesia is considered as a hallmark sign of neuropathic pain of the central sensitization type irrespective of the aetiology of the lesion to the nervous system (Loh and Nathan, 1978; Campbell et al., 1988a, b; Fields et al., 1998; Baumgärtner et al., 2002). Neurons in the dorsal horn of the spinal cord are sensitized to mechanical test stimuli by conditioning stimulation of nociceptive C-fibre afferents (Simone et al., 1991; Dougherty et al., 1998; Pertovaara, 1998). The resulting hyperalgesia has been termed “neurogenic hyperalgesia”, because it is induced by this afferent discharge and not by tissue injury itself (LaMotte et al., 1991). Due to the large receptive fields of spinal nociceptive neurons, neurogenic hyperalgesia involves large skin areas that may reach outside the boundaries of peripheral nerves or dermatomes. Central sensitization leads to enhanced spinal reflexes (Woolf, 1983; Grönoos and Pertovaara, 1993) and enhanced thalamocortical responses (Albe-Fessard et al., 1985; Lenz et al., 1998; Baron et al., 1999), both in animal models and in human subjects. Our observation of static mechanical hyperalgesia, together with previous evidence for enhanced spinal reflexes in RLS (Bara-Jimenez et al., 2000), provides evidence for central sensitization, probably within the spinal cord, in this syndrome.

Central sensitization in RLS may be based on afferent input-induced plasticity of spinal nociceptive transmission (Sandkühler, 2000). Long-standing abnormal peripheral input may explain various kinds of secondary RLS triggered by polyneuropathies (Salvi et al., 1990; Iannaccone et al., 1995; Gemignani et al., 1997; Gemignani et al., 1999; Polydefkis et al., 2000), radiculopathies (Walters et al., 1996), spinal stenosis (LaBan et al., 1990), diabetes (O’Hare et al., 1994), uraemia (Winkelmann et al., 1996; Collado-Seidel et al., 1998) or inflammatory diseases (Hemmer et al., 1995). In idiopathic RLS, however, there is no evidence of abnormal peripheral input as an underlying cause of central sensitization.

**Static versus dynamic mechanical hyperalgesia**

Mechanical hyperalgesia may be subdivided into two distinct subtypes (Koltzenburg et al., 1992; Ochoa and Yarnitsky, 1993): dynamic hyperalgesia assessed by stroking the skin with light tactile stimuli (alldynia), which is mediated by Aβ-fibre low-threshold mechanoreceptors normally responsible for touch sensations (Torebjörk et al., 1992; Treede and Cole, 1993) and static hyperalgesia (punctate hyperalgesia) assessed by pin-prick stimuli, which is mediated by nociceptive Aδ-fibre high-threshold mechanoreceptors (LaMotte et al., 1991; Ziegler et al., 1999; Magerl et al., 2001). Neurons in the dorsal horn of the spinal cord can be sensitized to both types of test stimuli by conditioning stimulation of nociceptive C-fibre afferents (Simone et al., 1991; Dougherty et al., 1998; Pertovaara, 1998). In contrast to typical neuropathic pain syndromes, RLS patients did not exhibit dynamic mechanical hyperalgesia to light touch (alldynia). The absence of alldynia may explain why central sensitization of the nociceptive system in RLS has been overlooked so far. In contrast to static hyperalgesia, dynamic hyperalgesia has been shown to be of shorter duration (LaMotte et al., 1991; Ziegler et al., 1999) and to depend on continuous conditioning input (LaMotte et al., 1991; Koltzenburg et al., 1994). Static mechanical hyperalgesia without dynamic mechanical hyperalgesia is sometimes reported in patients with neuropathic pain or in healthy subjects with secondary hyperalgesia, but in those cases, the degree of central sensitization as measured by the shift in stimulus-response function of pin-prick pain is usually mild (Baumgärtner et al., 2002). The shift in stimulus-response function in the present study, however, was by a factor of six in the lower limb, which exceeds that in many neuropathic...
pain patients. Thus, the absence of dynamic mechanical hyperalgesia is likely related to qualitative differences in the mechanisms of hyperalgesia-inducing pathophysiology of RLS compared with neuropathic pain.

**Restless legs as a pain modulation disorder—a possible role of dysfunctional descending control**

The gain of spinal nociceptive transmission is controlled in two principle ways, namely ascending afferent input-induced facilitation by vigorous or persistent peripheral nociceptive input (see above) and/or modification of the balance of facilitatory and inhibitory supraspinal descending control (Urban and Gebhart, 1999). Both mechanisms contribute to modification of the gain in spinal nociceptive transmission (Pertovaara, 1998). Thus, the increased gain of spinal nociceptive transmission in RLS may also result from dysfunctional descending control and be considered a pain modulation disorder as it is suspected for other widespread pain syndromes, e.g. the diffuse pain disorder seen in fibromyalgia patients (Gracely et al., 2002; Giesecke et al., 2003). In fact, both syndromes were reported to coincide (Yunus and Aldag, 1996; Tayag-Kier et al., 2000; Moldofsky, 2002). They share several symptoms, including sleep disturbances, periodic limb movements and widespread pain. Both exhibit female preponderance and similar neuroimaging results (San Pedro et al., 1998).

**Effects of acute and long-term dopaminergic treatment**

Lesions in the dopaminergic diencephalospinal tract (A11 neurons) have been proposed as an animal model for RLS (Ondo, 2000) and are discussed as the potential underlying cause of RLS in humans (Akpinar, 2003). The effects of acute dopaminergic treatment on RLS symptoms and long-term dopaminergic treatment on static mechanical hyperalgesia support this suggestion. Thus, the dopaminergic system is either directly or indirectly involved in the central sensitization in RLS, e.g. via restoration of sleep architecture (Akpinar, 2003), but imaging evidence points towards mild striatal dysfunction, suggesting a direct relationship of pain and decreased regional blood flow in the basal ganglia of RLS patients (San Pedro et al., 1998; for review see Garcia-Borreguero et al., 2003).

Dopamine is likely to exert a direct inhibitory influence on spinal nociceptive neurons by a descending dopaminergic pathway (Jensen and Yaksh, 1982; Jensen and Yaksh, 1984; Fleetwood-Walker et al., 1988; Liu et al., 1992), which is intermingled with descending noradrenergic fibres (Holstege, 1991). Dopaminergic mechanisms may also play a role in more rostral areas of the brain by controlling the descending pathways to the spinal cord, since dopamine-sensitive supraspinal structures involved in nociceptive processing encompass the mesolimbic reward circuit and the basal ganglia, especially the nucleus accumbens (Chudler and Dong, 1995; Altier and Stewart, 1999; Gear et al., 1999).

Dopaminergic mechanisms have already been implicated in processing of sustained pain in various animal models (Akil and Liebeskind, 1975; Dennis and Melzack, 1983; Lin et al., 1989). Likewise, human genetic and imaging studies suggest that either reduced dopamine availability and/or reduced dopamine receptor density will lead to increased pain perception, as well as a decrease in the capacity to modulate pain perception (Desautels et al., 2002; Hagelberg et al., 2002; Zubieta et al., 2003).

The role of dopamine in pain processing, however, is complex, because of a reciprocal regulation of the endogenous dopaminergic and opioidergic systems. Specifically, a high level of dopaminergic activity in the striatum reduces neuronal content of enkephalins and leads to a compensatory increase in μ-opioid receptor expression (George and Kertesz, 1987; Chen et al., 1993; Steiner and Gerfen, 1998; Zubieta et al., 2003). However, irrespective of the underlying mechanisms, the net effect of dopamine appears to be inhibition of pain perception, and the efficacy of dopamine as a non-classical analgesic is supported by a number of clinical reports on pain relief in breast cancer and bone metastasis (Dickey and Minton, 1972; Nixon, 1975), herpes zoster (Kernbaum and Hauchecorne, 1981), Parkinson’s disease (Quinn et al., 1986) and diabetic neuropathy (Ertas et al., 1998).

Dopaminergic substances with antinoceptive effects predominantly act at D2-receptors (Altier and Stewart, 1999; Magnusson and Fisher, 2000).

**Therapeutical aspects**

Besides the pathophysiological aspects, our findings may also be of therapeutic relevance. Glutamate acting at NMDA (N-methyl-D-aspartate) receptors and substance P acting at NK1 (neurokinin 1) receptors are assumed to be important mediators for the induction of central sensitization (McMahon et al., 1993; Urban et al., 1994; Chizh et al., 1997; Woolf et al., 1998). Thus, NMDA receptor antagonists and NK1 receptor antagonists may offer alternative therapeutic approaches in the treatment of RLS. First reports about the beneficial effect of the NMDA receptor antagonist amantadine in RLS support this hypothesis (Evidente et al., 2000). Other substances which are more commonly appreciated to alleviate RLS symptoms, such as opioids (Walters et al., 1993, 2001), anticonvulsants (Telstad et al., 1984; Happe et al., 2001; Thorp et al., 2001; Garcia-Borreguero et al., 2002) and the α2-agonist clonidine (Wagner et al., 1996), are also well accepted for the treatment of neuropathic pain (Sindrup and Jensen, 2000). Central sensitization as part of the pathophysiology of RLS may explain the beneficial effects of antinoceptive substances in treating RLS.
Conclusions
Our data show for the first time that RLS patients display static mechanical hyperalgesia to pin-prick. This type of hyperalgesia was significantly improved after long-term treatment with dopaminergic drugs. This observation allows us to speculate that RLS may be associated with central sensitization of spinal neurons due to abnormal peripheral input such as in chronic neuropathic pain and/or due to altered descending inhibition involving the supraspinal dopaminergic system. Thus, in addition to being a motor disorder, RLS may also be a pain modulation disorder with similarities to both neuropathic pain and the fibromyalgia syndrome.

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