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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

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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

Table 1 *Clinical characteristics of RLS patients*

Patient no.	Age (years)	Gender	Duration of RLS (years)	Family history	RLS therapy in patients available for follow-up	NCV	EMG	SL (min)	TST (min)	SE %	PLM index	PLMS arousal index	Improvement with 100 mg levodopa	
													Overall 'RLS symptoms' (before→after)	'Urge to move (before→after)
1	62	F	1	–	200 mg levodopa	Normal	nt	12	416	85	26	10	94→14	85→16
2	71	F	30	+	–	Normal	Normal	53	223	47	57	7	98→27	94→32
3	63	F	30	+	–	Normal	Normal	29	285	61	59	17	nt	nt
4	59	F	10	–	–	Normal	nt	70	295	64	27	20	nt	nt
5	57	F	20	–	1 mg cabergoline	Normal	nt	131	248	52	58	6	92→54	91→52
6	50	F	2	–	1 mg cabergoline	Normal	Normal	34	375	82	67	28	37→1	37→2
7	70	F	10	–	150 mg levodopa	Normal	nt	72	176	62	33	18	90→2	96→2
8	73	F	10	–	1.5 mg cabergoline	Normal	Normal	9	7	3	17	26	nt	nt
9	37	F	3	+	–	Normal	nt	13	400	87	6	1	82→46	83→43
10	63	M	40	+	–	Normal	nt	34	310	67	3	0	61→21	42→1
11	56	F	38	–	2 mg cabergoline	Normal	Normal	26	355	77	33	6	72→2	68→3

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.

et al., 1994). 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 polyneuropathy (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*., 1996), 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; Grönroos 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

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 B_{12} 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 dopamimetic 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

Pain 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

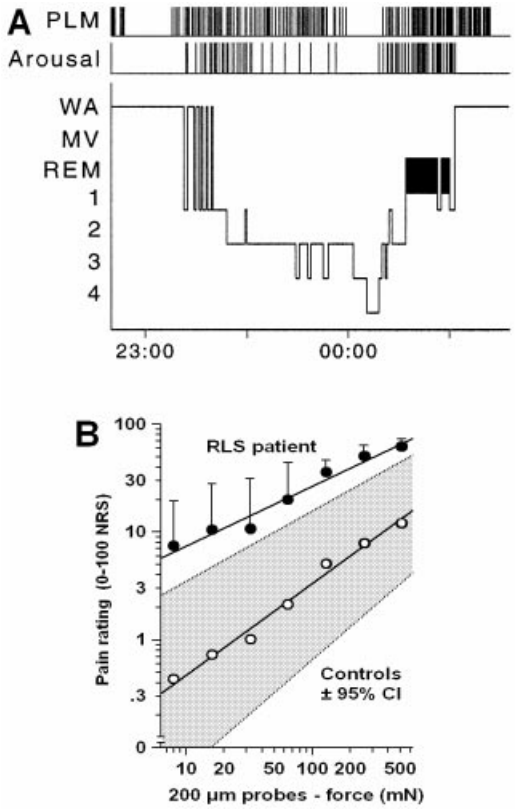

Fig. 1 Case example. This 50-year-old female patient suffered from RLS for 2 years. Her polysomnogram revealed a disturbed sleep structure with a decreased sleep efficiency resulting from a reduced total sleep time and a delayed sleep onset. Sleep was fragmented by frequent PLM during sleep (sleep stages 1, 2, 3, 4 and REM sleep) or wakefulness (WA) and PLM-related arousals as demonstrated in this 90-min fragment of the hypnogram (**A**). Blunt needles of different forces evoked graded intensities of pain. The stimulus-response function of pin-prick pain was above the 95% confidence interval for healthy age-matched subjects, indicating pronounced mechanical hyperalgesia (**B**) (data from stimulation of left and right feet combined). Values are mean ± SEM. MV = movement time; NRS = numerical rating scale.

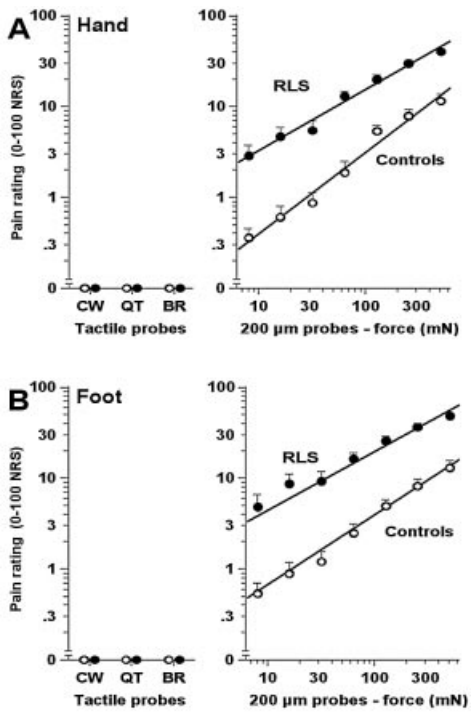

Fig. 2 Patients with RLS exhibit static hyperalgesia to pin-prick, but not dynamic allodynia. Stimulus-response functions of pin-prick pain in the hand (**A**) and foot dorsum (**B**) of patients with RLS (closed symbols) and age- and gender-matched control subjects (open symbols; $n = 11$, each). Pain evoked by the same set of graded punctate probes was about 5-fold stronger in RLS patients than in control subjects. Stroking with gentle tactile stimuli (CW = cotton whisp; QT = Q-tip; BR = brush) elicited no pain, i.e. in contrast to many neuropathic pain syndromes there was no allodynia in RLS patients. Values are mean ± SEM. NRS = numerical rating scale.

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

Factor	Degrees of freedom (effect, error)	*F*-value	*P*-value
Covariate: stimulus force	4, 302*	98.0*	<0.001
1: patients versus control subjects	1, 305	279.6	<0.001
2: hands versus feet	1, 305	51.8	<0.001
3: evening versus morning	1, 305	3.1	0.077
1 × 2 interaction	1, 305	3.8	0.054
1 × 3 interaction	1, 305	1.5	0.23
2 × 3 interaction	1, 305	0.0	0.96
1 × 2 × 3 interaction	1, 305	7.3	<0.01

*Calculated as multivariate ANCOVA (MANCOVA and Rao's *R* replacing *F*-value).

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

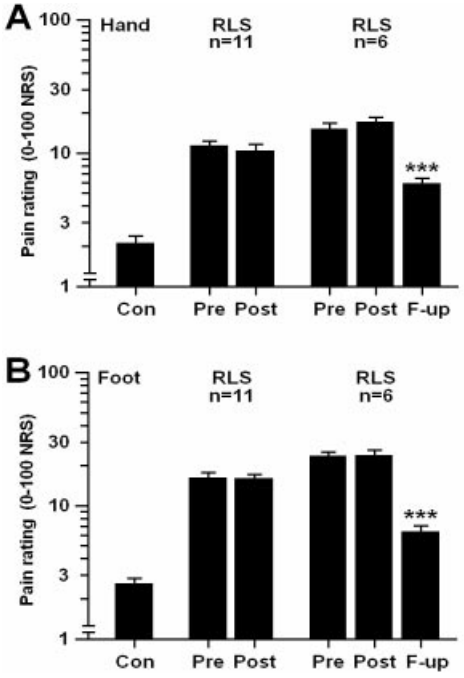

Fig. 3 Effects of dopaminergic treatment on pain perception in patients with RLS. Stimulus-response functions of pin-prick pain in the hand (**A**) and foot dorsum (**B**) were condensed into one mean rating value per patient (RLS) or healthy control subject (Con). On the first day after initiation of 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.

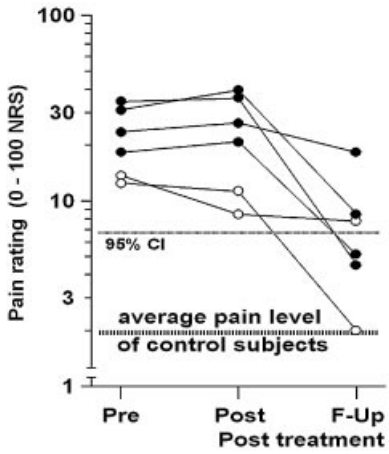

Fig. 4 Single-subject analysis of dopaminergic treatment effects on pain perception. Time course of pain perception before (Pre), immediately after (Post) and 12 months follow-up (F-up) after dopaminergic treatment ($n = 6$). Each data point represents the mean pain rating of one patient, averaged across all four limbs and all seven stimulus intensities. In half of the patients, follow-up pain ratings were within the 95% confidence interval of age-matched healthy subjects. Four patients were treated with the D2-receptor agonist cabergoline (filled circles) and two with L-dopa (open circles). NRS = numerical rating scale.

stronger hyperalgesia in the feet than in the hands (6.3× versus 5.4×; 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 dopamimetic 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 treatment in all patients (11 out of 11; acute treatment effect). A single evening dose of levodopa resulted in a significant relief of subjective RLS symptoms in all patients (Table 1). This subjective report could be quantified in a majority of the patients by means of a 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: $F(1,166) = 173.3$; $P < 0.001$; 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: $F(1\ 166) = 12.0$, $P < 0.001$). 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 underappreciated: 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*., 1988*a*, *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; Grönroos 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 (Winkelman *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 (allodynia), 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 (allodynia). The absence of allodynia 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 endogeneous 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 antinociceptive 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 therapeutical 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 antinociceptive 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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