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Pergolide restores sleep maintenance but impairs sleep EEG synchronization in patients with restless legs syndrome

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Abstract

Background: The treatment with the long-acting dopamine D1/D2 receptor agonist pergolide has been proven as very effective in lowering the frequency of periodic leg movements (PLM) in patients with restless legs syndrome (RLS). To further investigate the influence of this potent dopaminergic drug on the microstructure of rapid eye movement (REM) and non-REM sleep EEG we established a quantitative analysis of the EEG data.

Methods: The study group consisted of 15 patients with primary RLS (mean age 57.1 ± 10.1 years) who were a subgroup of patients within a double-blind randomized crossover treatment study with pergolide versus placebo. The polysomnographic recordings were analyzed visually and submitted to a quantitative EEG analysis (fast Fourier transformation).

Results: The pergolide treatment induced a significant reduction of the spectral power in the delta range (0.78–3.9 Hz; $P < 0.05$; *t*-test) during SWS, as well as a significant reduction of PLMs. In addition, we observed a decrease in the sigma EEG activity (12.1–14.8 Hz; $P < 0.03$) during non-REM sleep and stage 2 sleep. The visual sleep scoring revealed a significant increase in stage 2 sleep ($P < 0.005$), whereas wakefulness was markedly diminished ($P < 0.001$). The REM sleep parameters including the EEG power spectrum remained unchanged.

Conclusions: The treatment with pergolide markedly improved the sleep quality in RLS patients but did not restore SWS including the spectral power in the lower frequencies. Our results suggest that the dopamine agonist pergolide interferes with the subcortical mechanisms regulating the process of EEG synchronization during non-REM sleep. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Restless legs syndrome; Pergolide; Dopamine agonist; EEG synchronization; Spectral analysis

1. Introduction

The restless legs syndrome (RLS) is characterized by an irresistible urge to move the extremities due to strange and very uncomfortable sensory sensations, mainly dysesthesias or paresthesias in the lower limbs. Most of these patients suffer from additional involuntary and repetitive periodic limb movements during sleep (PLMs) and wakefulness including a circadian rhythmicity [1]. The treatment efficacy of dopaminergic drugs implies a dysfunction of the central dopaminergic neurotransmission as one of the underlying pathogenic factors. The treatment of first choice are currently the dopamine precursor levodopa and dopamine agonists including the strong long-acting dopamine D1/D2 receptor agonist pergolide [2–5]. More recent studies suggest a clinical efficacy of other dopamine agonists like pramipexole [6], ropinirole [7], and the combined dopamine-D2/α2 stimulant talipexole [8].

Despite of the overall improved subjective sleep quality about 20% of the patients reported a drug-induced insomnia under pergolide treatment [9,10]. A sleep-disrupting effect of drugs increasing the dopaminergic neurotransmission had been described repeatedly. Gillin et al. [11] already reported in 1973 that an infusion of Levodopa inhibited the occurrence of rapid eye movement (REM) sleep. A both REM- and slow wave sleep (SWS)-suppressive effect was shown for the strong dopamine D1/D2 receptor agonist apomorphine [12].

In our study using a double-blind and placebo controlled crossover design [4] we were able to confirm the clinical efficacy of pergolide in patients with RLS. Regarding the sleep architecture we observed a dramatic decrease in wake

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time whereas stage 2 sleep increased. However, the treatment with pergolide induced a significant decrease of the duration of SWS. The aim of the present study was to further clarify the differential effects of pergolide on the process of EEG synchronization during non-REM sleep. In order to investigate the microstructure of the sleep EEG, we established a sleep-stage specific quantitative analysis of the sleep EEG in a subset of patients of the study center in Munich.

2. Methods

2.1. Patient selection

The participants in the study were recruited from the outpatient clinic for movement and sleep disorders at the Max Planck Institute of Psychiatry in Munich, Germany. The protocol was approved by the Ethics Committee of the Bayerische Landesärztekammer in Munich. Written informed consent was obtained from all patients before they entered the study. Patients agreed not to take any psychotropic drugs (e.g. levodopa, dopamine agonists, benzodiazepines, opioids, carbamazepine, antidepressants, and neuroleptics) at least 2 weeks before baseline polysomnography and during the entire trial (except study medication). Before entering the study, all patients underwent a complete neurologic and general medical examination. Patients were included if they fulfilled the diagnostic criteria of the International RLS Study Group: (1) an irresistible urge to move associated with sensory complaints of the lower limbs, (2) motor restlessness, (3) worsening of the symptoms at rest with at least partial and temporary relief by activity, and (4) increased severity in the evening or at night. In addition, the symptoms had to have been stable for 2 weeks before the study. Baseline polysomnography had to reveal an abnormal PLM index (more than five PLMs per hour of time in bed). Based on clinical experience in the treatment of RLS, a sleep onset latency longer than 25 min or a sleep efficiency of less than 85%, or both, were also defined as baseline polysomnography inclusion criteria. Further details on patients inclusion or exclusion criteria are described previously [4].

2.2. Experimental design

The study was designed as a 12-week, double-blind, randomized, placebo-controlled clinical trial with two crossover periods. The study capsules contained either pergolide (0.05 mg) (Eli Lilly, Indianapolis, IN) or placebo. Unused capsules were returned to the project coordinator, who kept a record of all medication dispensed to and returned by the patients. Patients took pergolide or placebo once a day, 2 h before bedtime. The minimum dosage was 0.25 mg pergolide tid, the maximum dosage was 0.75 mg, respectively. To prevent peripheral dopaminergic side effects, all patients took 20 mg domperidone tid unblinded throughout the entire study beginning with the baseline period.

2.3. Polysomnography

Polysomnographic recordings of each patient were performed at baseline, with one night of adaptation, and at the end of both treatment periods. Patients were not allowed to nap during the day before the sleep investigation. Polysomnographic sleep recordings consisted of two EEGs (C3-A2/C4-A1, high-pass filter at 0.5 Hz, notch filter at 50 Hz), vertical and horizontal electrooculograms (EOGs), a submental electromyogram (EMG), an electrocardiogram (ECG) and EMGs of both anterior tibialis muscles. Polysomnographic recordings were carried out from 23:00 (lights out) to 07:00 h (lights on). Sleep stages were scored visually by experienced raters for consecutive 30-s epochs according to the standardized criteria [13]. The PLMs were scored during both sleep and wakefulness in accordance with international scoring rules [14]. The total number of PLMs, the number of PLMs per hour of time in bed (PLM index), and the number of PLMs during sleep (PLMS) were calculated. Arousals or leg movements after single respiratory events (apneas or hypopneas) were excluded from the calculations.

2.4. Spectral analysis of sleep EEG

The EOG, EEG, EMG, and ECG signals were filtered and transmitted to the polygraph (Schwartzer, ED 24). The digitized data (8-bit analog-to-digital converter, sampling rate 100 Hz) were stored on the disk and calibrated with a 50-μV 10-Hz sine wave. The C3-A2 EEG derivation was subjected to spectral analysis using a fast Fourier transformation. The sleep-stage specific EEG power spectra were computed as described previously [15]. The frequency resolution was set to 0.39 Hz between 0 and 48.3 Hz inclusively. To exclude possible aliasing due to the filter settings, analysis was restricted to between 0.78 and 19.1 Hz. Artifacts, for example, those caused by brief body movements, were excluded manually by referring to the EEG recordings. The EEG activities of the 50 frequency bins were cumulated across the delta (0.78–3.9 Hz), theta (4.3–7.8 Hz), alpha (8.2–11.7 Hz), sigma (12.1–16.0 Hz) and beta (16.4–19.1 Hz) range.

2.5. Statistical analysis

The sleep variables derived from standard visual scoring, power densities obtained by the spectral analysis of the sleep EEG, and the indexes of PLMs were tested about significance by Student's paired *t*-test between placebo and pergolide treatment using StatView version 5.0 (SAS Institute). $\alpha = 0.05$ was accepted as the nominal level of significance. We calculated the power densities of the sleep state specific mean value of the total night for band ranges and frequency bins. The statistical comparisons were done separately for sleep stage 2, non-REM sleep (sleep stages 2,

Table 1
Effect of pergolide on sleep parameters and periodic leg movements (PLMs)[a]

Variable	Placebo	Pergolide	*P*
Time in bed (min)	474.3 ± 20.1	482.1 ± 7.6	n.s.
Sleep period time (min)	425.8 ± 61.8	448.2 ± 24.2	n.s.
Total sleep time (min)	269.6 ± 110.5	372.1 ± 66.2	< 0.01
Sleep efficiency (%)	61.1 ± 22.8	82.7 ± 13.2	< 0.01
Sleep onset latency (min)	38.5 ± 65.2	21.3 ± 18.3	n.s.
No. of awakenings	24.1 ± 13.7	25.7 ± 12.0	n.s.
Stage 1 (min)	36.9 ± 18.6	43.2 ± 24.6	n.s.
Stage 2 (min)	175.8 ± 79.9	260.6 ± 48.8	< 0.01
Slow wave sleep (min)	8.9 ± 13.6	8.7 ± 14.6	n.s.
REM (min)	47.6 ± 24.7	58.2 ± 24.1	n.s.
Wake (min)	172.2 ± 84.7	98.4 ± 58.0	0.001
REM sleep latency	182.5 ± 97.1	120.2 ± 79.4	n.s.
REM density	2.3 ± 0.8	2.5 ± 1.2	n.s.
No. of PLMs	417.4 ± 307.3	51.4 ± 44.1	< 0.001
No. of PLMs during wake	6.1 ± 7.3	1.3 ± 2.2	< 0.05
No. of PLMs during sleep	411.3 ± 305.3	50.1 ± 43.0	< 0.001
PLM index/h	52.4 ± 37.9	6.4 ± 5.5	< 0.001
PLM index during wake/h	3.5 ± 5.7	1.2 ± 1.9	n.s.
PLM index during sleep/h	96.4 ± 77.0	7.9 ± 6.6	< 0.001

[a] Data are given as mean ± SD; differences between the experimental conditions were tested by Student's paired *t*-test. n.s., not significant.

3 and 4), SWS (sleep stages 3 and 4), and stage REM sleep. Due to the bad sleep quality in the placebo condition the analysis of the EEG data during SWS had to be restricted to six patients.

3. Results

3.1. Subjects and dosage

Fifteen patients (eight men, seven women; mean age 54.4 ± 9.7, range 29–71 years) completed the study. The mean duration of the disease was 18.2 ± 10.4 years (range 2–36 years). Four patients had been never treated, and 11 patients had been treated with L-DOPA (mean dosage 386.4 ± 205.1 mg, range 200–800 mg). The mean pergolide dosage at the end of each crossover period was 0.55 ± 0.21 mg tid (range 0.25–0.75 mg tid).

3.2. Sleep variables and spectral analysis of sleep EEG

Table 1 is listing the treatment effects on the parameters of sleep continuity, sleep architecture and PLM indexes. The treatment with pergolide resulted in a marked improvement of the sleep efficiency due to the dramatic suppression of the number of PLM during sleep. Regarding the sleep architecture the treatment with pergolide significantly reduced the duration of wakefulness though the frequency of nocturnal awakenings remained similar between both conditions. Stage 2 sleep was significantly increased whereas the duration of SWS and the REM sleep parameters (REM latency, duration, REM density) were not affected by the treatment.

Fig. 1 shows the effects of pergolide on the all-night EEG power spectrum during non-REM sleep and REM sleep. In general, the pergolide treatment induced an overall reduction of the spectral power densities during non-REM sleep. In particular, we observed a reduction of the EEG activity in the slow wave and sigma frequency range representing the sleep slow waves and sleep spindles, respectively.

The all-night mean spectral power within the delta (0.78–3.9 Hz), theta (4.3–7.8 Hz), alpha (8.2–11.7 Hz), sigma (12.1–16.1 Hz) and beta (16.4–19.1 Hz) ranges during the corresponding sleep stages are given in Fig. 2. The administration of pergolide resulted in a significant decrease of the sigma EEG activity during non-REM sleep (Student's paired *t*-test: $P = 0.002$), and also during stage 2 sleep ($P = 0.002$). Moreover, there was a significant decrease of the delta EEG activity during SWS ($P = 0.049$). In contrast, the spectral profiles during REM sleep were not significantly influenced by the treatment.

4. Discussion

The treatment with pergolide significantly improved the subjective sleep quality in RLS patients which was obviously due to the dramatic suppression of PLM/S and consecutive reduction of nocturnal wakefulness. Thus, we could confirm previous results proving that the administration of the potent and long-acting dopamine D1/D2 receptor agonists pergolide is a clinically very efficient treatment of RLS [2,4,16]. Using advanced techniques to describe the microstructure of sleep we were able to detect a pergolide-induced impairment of the EEG synchronization during non-REM sleep that is putatively independent from the beneficial effects of the drug on the nocturnal motor activity.

The conventional sleep staging showed that the administration of pergolide improved sleep fragmentation and significantly increased stage 2 sleep, though the amount of SWS

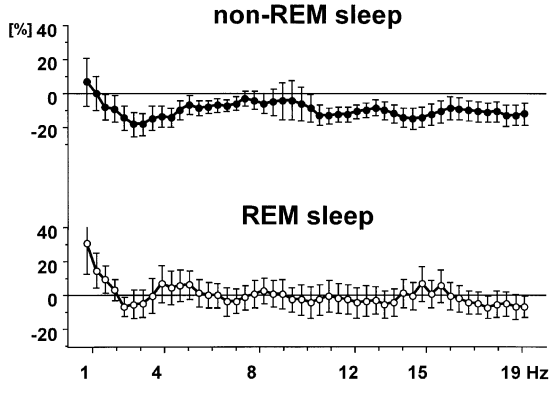

Fig. 1. EEG power spectrum of non-REM and REM sleep. Effects of pergolide on the power densities (0.78–19.1 Hz) of non-REM sleep and REM sleep during the night sleep ($n = 15$). The data represent the mean (±SEM) deviation from the placebo condition (= 0%).

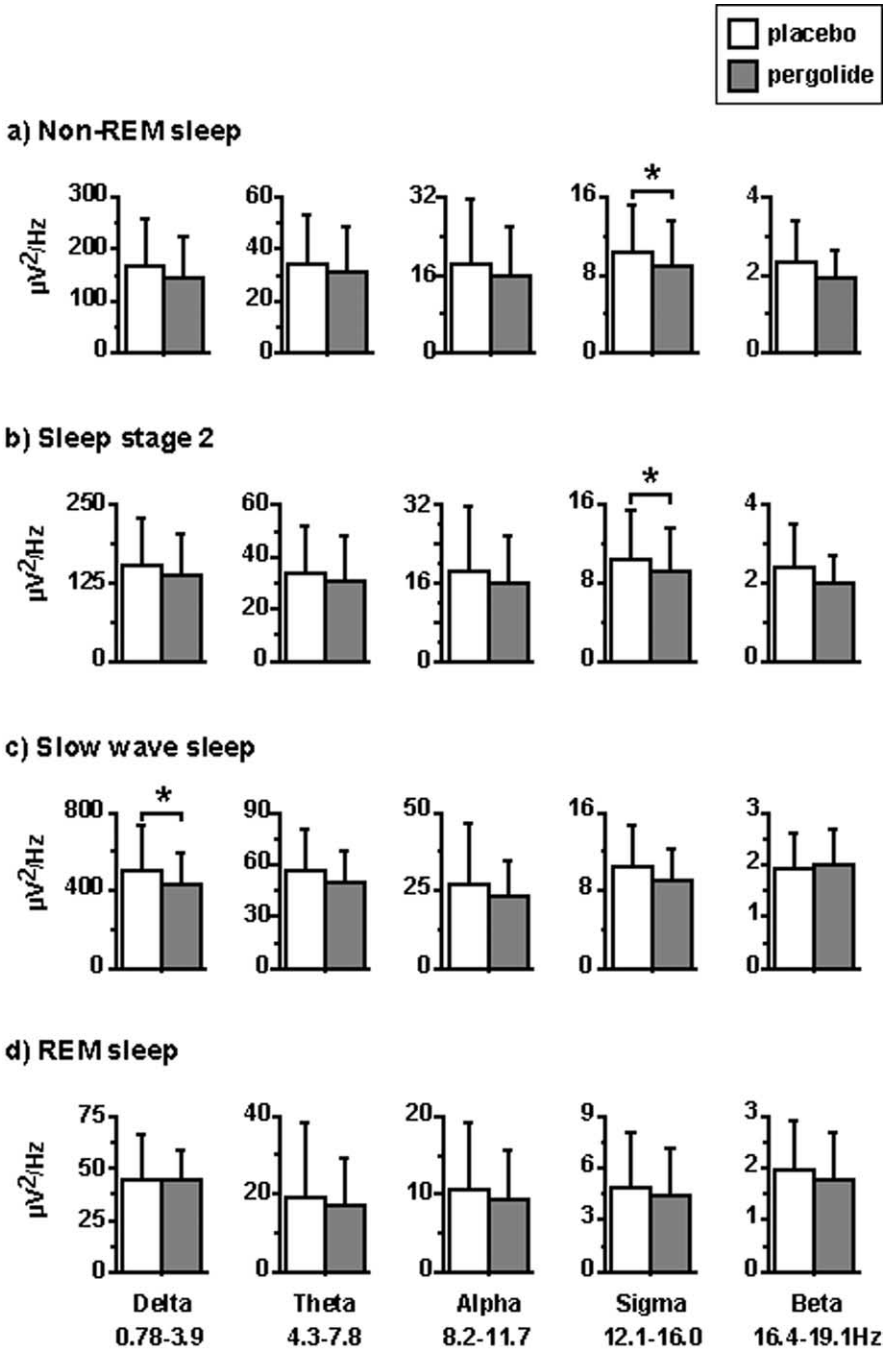

Fig. 2. Sleep stage specific comparisons. Effects of pergolide on the average (mean ± SD) EEG activities within the delta (0.78–3.9 Hz), theta (4.3–7.8 Hz), alpha (8.2–11.7 Hz), sigma (12.1–16.1 Hz) and beta (16.4–19.1 Hz) range during (a) non-REM sleep ($n = 15$), (b) stage 2 sleep ($n = 15$), (c) SWS ($n = 6$), and (d) REM sleep ($n = 15$). Asterisks indicate significant differences between placebo and pergolide treatment ($P \leq 0.05$, Student's paired t-test).

was slightly reduced [4]. In line with that, the quantitative analysis of the EEG data demonstrated a significantly reduced amount of slower frequencies. However, the observed decrease in sigma frequencies was somewhat surprising with respect to the enhanced amount of visually scored stage 2 sleep. This sleep stage is usually characterized by the pronounced occurrence of sleep spindles resulting in predominant peaks in the corresponding sigma EEG activity [17]. The discrepant results obtained by the visual scoring and the quantitative EEG analysis may be therefore due to methodological aspects. The conventional scoring of sleep stage 2 is based on the occurrence but not the quantity of sleep spindles. Thus, despite of a reduced amount of sleep spindles it is possible to score stage 2 sleep due to the other EEG criteria defining this sleep stage [13]. On the other hand, the non-REM sleep specific EEG power spectrum provided evidence that the treatment with pergolide suppressed both the slower and the sigma frequencies. Therefore, only the

additional analysis of the quantitative EEG data revealed that pergolide restored the sleep maintenance but appeared to interfere with the EEG synchronization process during non-REM sleep. In contrast, the REM sleep parameters including the REM sleep specific EEG power spectrum remained fairly unchanged by the treatment.

In view of the previous literature on the interaction of dopamine with the sleep generating mechanism it is speculated that the drug-related effects on the movement disorder and the impaired EEG synchronization are not related to each other. According to the current hypothesis PLMs triggered by quiet wakefulness or sleep are due to a disinhibition of the descending inhibitory pathways projecting from the cerebellum and brainstem to the spinal cord level [18,14,19]. The dopaminergic system appears to be critically involved in the sleep-related motor control since dopaminergic drugs efficiently suppress PLMs. Patients with Parkinsonian syndromes may develop a REM sleep behavior disorder including an insufficient muscle atonia during REM sleep [20].

On the other hand, numerous studies on the sleep EEG effects of this and other dopamine-active substances have established a dose-dependent modification of the sleep architecture where both slow wave and REM sleep are suppressed by high doses of either levodopa [11], apomorphine [12], but also specific dopamine D1- [21], D2- [22], or D3-receptor agonists [23]. Conversely, subclinical low dosages of the substances promote EEG synchronization during wakefulness, and slow wave or REM sleep, respectively [24,25].

Neurophysiological research in animals provided evidence for a potent dopaminergic control of the thalamocortical circuits that are crucial for the sleep-associated EEG synchronization [26]. With regard to the receptor subtypes dopamine D1 and D2 receptors have been characterized in various thalamic cell groups [27–29]. With respect to the current concepts on the cellular bases of EEG spindles and delta waves, it is of special interest that dopamine D1 receptors were identified on GABAergic neurons of the reticular thalamic nuclei [30] that control the disinhibition of the ascending excitatory projections. Concerning the D2 receptor systems the activation of either presynaptic autoreceptors and/or postsynaptic receptors may mediate the dose-dependent biphasic EEG effects in terms of a sedation (low dopamine concentrations) or EEG desynchronization inducing behavioral arousal (high dopamine concentrations), respectively [24,25,31]. The latter is a well-known clinical phenomenon during the treatment with dopamine agonists in patients with Parkinson's disease [32]. Therefore, the observed impairment of EEG synchronization by pergolide is interpreted as an extrastriatal and short-term central pharmacological effect of the drug. In detail, it may be speculated that the pergolide-induced EEG desynchronization is due to an activation of the thalamic dopamine D1- and D2 receptor, i.e. the D1 receptors on the GABAergic neuron in the reticular thalamic nuclei.

Our data could not confirm a REM sleep-suppressive effect of pergolide since none of the REM sleep parameters nor the spectral profiles of REM sleep appeared to be influenced by the present dosage of the drug.

In summary, the increased sleep quality but impaired sleep depth suggests that pergolide rather improves the motor symptoms and the PLM-associated sleep fragmentation than the underlying sleep disorder of this disease [33]. Long-term follow-up investigations are necessary to clarify the clinical significance of the observed effects on the sleep-generating mechanisms.

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