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Original Article

Changes of cortical excitability after dopaminergic treatment in restless legs syndrome

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ABSTRACT

Objective: Dopaminergic pathways are most likely involved in the pathophysiology of restless legs syndrome (RLS). In previous investigations, an alteration of cortical excitability was suggested to be related to a dopaminergic dysfunction in RLS. The purpose of our study was to compare practice-dependent plasticity in RLS patients before and after a month of dopaminergic treatment.
Methods: Single-pulse transcranial magnetic stimulation (TMS) was used to define motor evoked potential (MEP) amplitude, motor threshold, and silent period (SP) as well. Subjects performed three exercise blocks (bimanual motor task). MEP amplitude, registered immediately after each exercise block and after a rest period, was compared to baseline. The time course of intra-cortical inhibition was tested using paired-pulse TMS at short inter-stimulus intervals. For the single-pulse TMS procedures, we enrolled 12 patients affected by primary RLS and 12 normal subjects. For the paired-pulse TMS procedures, only six patients underwent the examination. RLS patients underwent the examination in both pre- and post-dopaminergic treatment conditions.
Results: In RLS patients MEP amplitude increased after the rest period only in the post-treatment condition, showing a delayed facilitation. After exercise, MEP amplitude increased, but not enough to be significant, showing a positive trend but not a clear-cut post-exercise facilitation. In the pre-treatment condition instead, MEP amplitude did not change either after rest period or after exercise.
Results: RLS patients showed a marked increase of the central motor inhibition, assessed by using paired-pulse TMS at short inter-stimulus intervals after pramipexole treatment. On the contrary, the duration of the SP did not change compared to the pre-treatment condition.
Conclusions: In RLS patients after dopaminergic treatment, the main finding was the changing of MEP amplitude after rest following a motor task. Since dopaminergic treatment can reverse delayed facilitation in RLS, we hypothesized that cortical plasticity related to dopaminergic systems may play a crucial role in RLS pathophysiology.

1. Introduction

Patients affected by restless legs syndrome (RLS) usually complain of an unpleasant sensation in the legs and sometimes in the arms, which becomes evident during evening and night rest, associated with an irresistible urge to move. As no laboratory or RLS-specific clinical tests are available, diagnosis is based on the presence of specific clinical symptoms. Likewise, the exact pathophysiology of RLS still remains unknown [1,2].

The dopaminergic system seems to be involved in the pathophysiology of RLS mainly because dopamine-receptor agonists can successfully treat the symptoms of RLS [2–4] and also because a variety of alterations in dopaminergic function has been demonstrated in RLS patients. Some of these alterations have also been found through positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) [5,6]. These findings, however, are not peculiar in RLS; in fact, they can also be observed in other clinical conditions. Transcranial magnetic stimulation (TMS) may be used to study the movement-related cortical plasticity and the intra-cortical inhibition both in healthy and unhealthy subjects. In healthy subjects, motor evoked potential (MEP) amplitude increases immediately after a brief period of exercise ("post-exercise facilitation" phenomenon) and then increases again after a rest period of 15 min following a defined motor task ("delayed facilitation" phenomenon) [7–10]. The mechanism for post-exercise facilitation is thought to be due to a transient increase of excitability in the motor cortex [7,8]. The delayed facilitation seems to reflect an intra-cortical synaptic reorganization consequent to the performance of repetitive motor tasks

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[9,10]. Although the mechanism underlying this form of cortical plasticity remains to be determined, we suggested that the motor task could induce enduring changes in synaptic strength, in this way improving motor learning [9,10]. In healthy subjects, the presentation of a conditioning TMS pulse shortly before a test pulse reduces MEP amplitude of the test pulse itself, which could be interpreted as an expression of the intra-cortical inhibition [11]. In addition, immediately after the MEP, muscle contraction is followed by a period of electrical silence that causes discontinuation of the ongoing EMG activity; this phenomenon is named "silent period." The silent period may be considered an indicator of inhibitory activity within primary motor cortex [12–14]. A few studies have used TMS to investigate the central motor system in RLS patients [15–20]. Despite some inconsistencies, the authors conclude that the pyramidal tract is intact in RLS patients, whereas the motor cortical excitability is altered, suggesting a cortical–subcortical origin of the disease. Methodological differences may account for some of the inconsistency among the studies. In particular, in our studies [19,20], we showed some modifications in movement-related cortical plasticity and intra-cortical inhibition. In RLS patients, we demonstrated the absence of delayed facilitation, the absence of post-exercise facilitation, a shortening of the silent period and a reduction of intra-cortical inhibition as well.

We speculated that the above mentioned findings, identified in RLS patients by means of TMS, could be related to an alteration of the cortical plasticity resulting from a dopaminergic dysfunction [19].

We compared motor cortex excitability in RLS patients in basal condition and after a month of pramipexole therapy (a non-ergot dopaminergic agonist) to confirm these hypotheses and to determine whether dopaminergic treatment can restore normal TMS findings in RLS.

2. Methods

2.1. Patients

Twelve right-handed patients (8 women and 4 men, mean age 52.67 ± 10.9 years), affected by primary (idiopathic) RLS, were included in our study and submitted to TMS. A complete neurophysiologic investigation (electromyography with nerve conduction study, F waves, soleus H reflex) was carried out in all patients in order to exclude peripheral nervous system involvement. All RLS patients fulfilled the criteria for a diagnosis of primary RLS according to the International RLS Study Group criteria [1,2]. Patients had never previously taken any medications known to affect the TMS results; in particular, they had never been treated with dopaminergic or anti-dopaminergic drugs before the study. All patients had experienced symptoms compatible with a diagnosis of RLS for at least 1 year. Pramipexole was administrated over a period of 4 weeks. The starting dose was 0.125 mg/day, which was then doubled in 1–2 weeks (final dose 0.25 mg/day). Patients received treatment once daily, 1 or 2 h before bedtime. All patients tolerated the treatment without major adverse events or complaint. Signed informed consent forms were obtained from all subjects.

2.2. Controls

A control group included 12 age- and sex-matched (6 women and 5 men, mean age 49.4 ± 3.1 years), right-handed normal subjects who were drug free with no history of neurologic problems or psychiatric illness.

2.3. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was performed with a MagLite-r25-Twin Top, Medtronic A/S biphasic stimulator (Copenhagen, Denmark) using single- and paired-pulse procedures. We stimulated the non-dominant hemisphere because we observed that delayed facilitation in healthy subjects is limited to this hemisphere (personal observations) [10] and also because an interhemispheric asymmetry in the excitability of cortical inhibitory mechanisms has been demonstrated [21].

According to the experimental design, the assessment of patients' motor cortex excitability was performed separately in two different conditions: basal (pre-treatment condition) and after a month of dopaminergic therapy (after-treatment condition). In both conditions, in order to prevent the effect of circadian factors, evening somnolence, peak of RLS symptoms, and acute effect of pramipexole, the recording sessions were always performed late in the morning following a full night of spontaneous sleep. In order to avoid vigilance fluctuations, the subjects under TMS session were asked by the investigator to remain on alert with open eyes, but in a relaxed body condition.

The controls were studied only in basal condition.

2.4. Experimental procedures

The TMS protocols we performed have already been described in detail in a recent paper [19].

In summary, the following three experimental sessions were performed for each condition (pre-treatment and post-treatment). (1) Evaluation of MEPs parameters: motor threshold, MEP amplitude, and silent-period duration were measured in response to single-pulse magnetic stimulation [12,13,19]. (2) Motor task: MEPs were recorded in response to single magnetic stimuli after a motor task [9,10,19,20]. (3) Paired-pulse stimulation: the time course of intra-cortical motor activity was tested using pairs of magnetic stimuli (1–6-ms inter-stimulus intervals) [11,19].

2.4.1. Single-pulse TMS: MEP amplitude, motor threshold, and silent period

MEPs were recorded from the first dorsal interosseous muscle of the left non-dominant hand via surface electrodes applied in a belly-tendon montage. A round coil (90 mm) was used, and the lateral edge was placed over the presumed hand area. The coil handle was held backward in a lateral (45°) direction from the inter-hemispheric line [11,13,19]. The optimal scalp position was determined by moving the coil in 1-cm steps over the presumed hand motor area. The site where the optimal MEP amplitude was elicited during muscle relaxation with the lowest threshold was marked and used for later testing. For motor threshold measurement, MEPs were recorded during relaxation of the target muscle [13,16]. A moderate contraction allowed the detection of both MEP and silent-period parameters in the 500 ms following TMS. Stimulus intensity during testing was determined by adding intensity equal to 5% of the maximum stimulus output above the motor threshold. The mean of three consecutive trials was used to define the following parameters:

- Motor threshold (%), defined as the intensity required to elicit detectable MEPs with amplitudes of 0.05–0.15 mV in 50% of the stimuli. It was expressed as the percentage of the stimulator's maximal output [13].
- MEP amplitude (mV), defined as the peak-to-peak amplitude between the largest negative and positive deflections following stimulus onset [13].
- Silent-period duration (ms), measured from the MEP to the rebound of voluntary electromyogram (EMG) activity (absolute duration of silent period) [14,15,19]. The EMG was recorded with 0.5-mV gain sensitivity, and the analysis time ranged from 200 to 500 ms.