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Non-homogeneous effect of levodopa on inhibitory circuits in Parkinson's disease and dyskinesia

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ABSTRACT

Introduction: Levodopa-induced dyskinesia in patients with Parkinson's disease (PD) has been shown to be associated with an abnormal plasticity in the motor cortex. We investigated whether changes in the excitability of inhibitory and excitatory motor circuits could underlie maladaptive mechanisms associated with dyskinesia.
Methods: Using single and paired transcranial magnetic stimulation (TMS), we studied motor threshold, silent period (SP) duration, intracortical facilitation (ICF), short intracortical inhibition (SICI) and low- and high-intensity long intracortical inhibition (LICI) in 10 dyskinetic and 10 non-dyskinetic patients, matched for disease and treatment duration, before (OFF state) and after (ON state) levodopa, and in 10 healthy controls.
Results: In the OFF state, the two groups of patients showed similar motor cortex excitability with a reduced SICI compared to controls. LICI was weaker and increasing stimulation intensity had a lower effect on SP duration in dyskinetic patients than in controls. In dyskinetic patients, in contrast to non-dyskinetic patients, levodopa failed to increase SICI and SP duration, and potentiated to a lesser extent the effect of increasing the stimulation intensity on LICI. Although levodopa improved motor symptoms to a similar extent in both dyskinetic and non-dyskinetic patients, it failed to activate effectively the excitability of the inhibitory systems in dyskinetic patients.
Discussion: These findings suggest that dyskinesia is associated with an abnormal effect of levodopa on cortical motor inhibitory circuits.

1. Introduction

Levodopa is an effective treatment in Parkinson's disease (PD), but its beneficial effect is often jeopardized after a few years of use by the occurrence of dyskinesia. Although its pathophysiology remains unclear, dyskinesia has been associated with an abnormal form of plasticity in motor circuits in animal models of PD [1]. Some transcranial magnetic stimulation (TMS)-based procedures have been developed to induce long term potentiation (LTP) and long term depression (LTD)-like plasticity in the primary motor cortex of PD patients. In PD patients with a stable response to dopaminergic treatment, both types of plasticity can be induced even when patients are deprived of treatment (OFF state) [2]. In contrast, in patients that have developed motor fluctuations with or without dyskinesia, such plasticities are more difficult or even impossible to induce in the OFF state [2,3]. Among these patients, marked differences were observed between dyskinetic and non-dyskinetic patients when cortical plasticity was analyzed under the effect of levodopa. Unlike in non-dyskinetic patients, LTP was impossible to restore in a paired associative stimulation protocol [3] or unresponsive to a depotentiation protocol after having been induced by an excitatory theta burst stimulation mode [4] in dyskinetic patients. A paradoxical effect was even observed after an acute administration of levodopa in dyskinetic patients with an LTP-like

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response obtained with an inhibitory theta burst stimulation mode [2]. These different studies suggest that dyskinesia might be associated with changes in motor cortex excitability.

Using TMS, previous studies have found changes in motor cortex excitability of PD patients when compared to healthy subjects [5]. Most of these changes are reversed by dopaminergic treatment [6,7]. In the present study, we used TMS to investigate the excitability of inhibitory and excitatory circuits in patients with and without dyskinesia and tested the hypothesis that an aberrant inhibition or an abnormal effect of levodopa on motor cortex excitability is associated with dyskinesia.

2. Subjects and methods

2.1. Subjects

We studied 20 PD patients with motor fluctuations, with ($n = 10$) or without ($n = 10$) daily dyskinesia, and 10 healthy controls. The dyskinetic and the non-dyskinetic patients fulfilled the United Kingdom Parkinson's disease brain bank criteria for PD [8] and were matched for disease and treatment duration. They were all receiving levodopa, which was administered in association with a dopamine agonist in 17 patients; the treatment had been stable for at least 1 month before the study. Patients with marked tremor, cognitive decline or markedly impaired balance were not included in the study. All were right-handed according to the Edinburgh Handedness Inventory. The experimental protocol was approved by the Grand-Ouest Ethics Committee (Nantes, France) and all the participants gave their written informed consent. The patient's clinical characteristics are shown in the table.

The two groups of PD patients were studied during one single session in two states: the practically defined "OFF" state, after overnight withdrawal of anti-parkinsonian medication; and the "ON" state, at the time of maximal clinical benefit, reached about 45 min after administration of liquid levodopa (patient's usual first morning levodopa equivalent dose plus 50 mg). PD symptoms were assessed in both conditions with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III) and the modified Hoehn and Yahr scale. UPDRS III was assessed just before TMS and immediately after TMS to verify the stability of the parkinsonian state. Dyskinesia was rated with UPDRS IV (items 32–34) and with a scale of severity [9].

2.2. TMS protocol

TMS was performed with a 90-mm round coil and two Magstim 200 stimulators connected to a BiStim module (Magstim, Whitland, UK). The coil was centered over the vertex with a monophasic current flowing anticlockwise when viewed from above to activate the left hemisphere. The coil was reversed for stimulation of the right hemisphere. The coil was held in a fixed position by a mechanical arm over the optimal scalp position for eliciting the largest motor evoked potential (MEP) in the abductor digiti minimi (ADM) of the patient's more affected arm and the dominant side for controls. MEPs were recorded using surface bar electrodes fixed on the skin with a belly-tendon montage. Signals were amplified using a Nicolet Bravo (Nicolet Biomedical, Madison, WI), filtered (band pass 30 Hz to 3 kHz), digitized at 5 kHz and stored for off-line analysis. Electromyography (EMG) activity was monitored continuously with audio and visual feedback at a sensitivity of 50 μV/division to ensure the absence of voluntary background activity.

Cortical excitability was studied with fully relaxed ADM. The resting motor threshold (RMT) was defined as the lowest percentage of the stimulator output able to elicit an MEP of >50 μV in at least five out of ten consecutive trials. Paired-pulses were applied at two interstimulus intervals (ISIs) of 3 and 15 ms to investigate short intracortical inhibition (SICI) and intracortical facilitation (ICF), respectively [10], and at long ISIs (100 ms) to analyze long intracortical inhibition (LICI). For each ISI, the conditioning stimulus (CS) preceded the test stimulus (TS). For SICI and ICF, the CS and TS were set at 80% and 120% of the RMT, respectively. For LICI, CS and TS were delivered at the same intensities and two intensities, 120% and 180% of RMT, were tested. The mean peak-to-peak MEP amplitude was calculated from 4 reproducible trials (about 10 trials were performed) by measuring MEP amplitudes. The averaged conditioned MEP amplitude was expressed as a percentage of the averaged unconditioned MEP (TS alone for SICI and ICF; CS for LICI) amplitude assigned at 100%. SP duration was measured during an isometric contraction of approximately 20% of maximum voluntary contraction. Subjects were asked to relax between each measure and the EMG activity was controlled by audio-visual feedback. The stimulator intensity was raised from 10% to 100% of maximum stimulator output in 10% increments. Three reproducible trials were performed for each intensity. SP duration was measured from the onset of stimulation artifact to the first return of voluntary EMG activity.

2.3. Statistical analysis

A linear mixed model was used for SP analysis with subject as a random effect and stimulus intensity (10 intensities from 10% to 100%) and group (dyskinetic or non-dyskinetic patients), in both the OFF and ON states, as independent variables. If the factor group showed a significant main effect, it was further explored with a conditional logistic regression at each intensity. The effect of levodopa on SP was studied with a separate linear mixed model in each PD group, with intensity and state (OFF or ON) as independent variables. If the factor state was significant the effect was explored with the Wilcoxon signed rank test at each intensity. Additional separate linear mixed models were performed to compare the SP duration in dyskinetic or non-dyskinetic patients with controls. If the factor group showed a significant main effect, this effect was explored with a Mann–Whitney U test at each intensity. For the other TMS parameters and motor UPDRS motor score, a conditional logistic regression was used to compare dyskinetic with non-dyskinetic patients in both OFF and ON states. Each group of patients was compared separately to controls with a Mann–Whitney U test. Separate analyses were performed for each treatment condition, i.e. the ON and OFF states. For LICI analysis, the Wilcoxon signed rank test was used to compare the amplitude of the control and conditioned MEP responses at each intensity for all groups of subjects and in both OFF and ON states for the patients. For the comparisons of TMS parameters between the two groups of patients in the OFF state, additional analyses were performed with an adjustment for the UPDRS motor score. The open source software R (version 2.5.1) was used for statistical analyses (R Development Core Team, 2005), and the level of significance of all tests was fixed at 0.05.

3. Results

Dyskinetic and non-dyskinetic patients did not differ in terms of duration and severity of PD and of antiparkinsonian treatment. The age was not different between controls (54.4 ± 1.9 years) and the two groups of patients (Table 1).

The administration of levodopa (dyskinetic: dosage = 310 ± 60 mg; non-dyskinetic: 270 ± 60 mg) improved motor signs in dyskinetic (69 ± 4% decrease of the UPDRS III score in ON *vs.* OFF state, $P < 0.01$) and in non-dyskinetic (66 ± 4%, $P < 0.01$) patients (Table 2). Mild to moderate dyskinesia was observed in all dyskinetic patients at the peak-dose effect of levodopa while none were observed in the non-dyskinetic patients (Supplementary Table 1).

RMT was similar among the groups of subjects and there was no effect of the levodopa in either group of patients (dyskinetic: 48.0 ± 2.9% in the OFF state, 48.5 ± 2.8% in the ON state; non-dyskinetic: 53.0 ± 2.2% in the OFF state, 51.0 ± 2.4% in the ON state; controls: 51.5 ± 1.1%).

3.1. Short intracortical inhibition and intracortical facilitation

Test MEP amplitude (~0.3 mV) did not differ among the groups. In the OFF state, the two groups of patients showed a reduction of SICI (dyskinetic: 49.5 ± 7.6%; non-dyskinetic: 48.05 ± 7.6%) compared to controls (28.8 ± 4.7%, $P < 0.05$).

Levodopa increased SICI only in non-dyskinetic patients (OFF state: 48.05 ± 7.6% *vs.* ON state: 30.9 ± 4.01%, $P < 0.05$) and had no significant effect in dyskinetic patients (OFF state: 49.5 ± 7.6% *vs.* ON state: 44.8 ± 9.5%) (Fig. 1).

In the OFF state, ICF was slightly lower in the two groups of patients (dyskinetic: 141.7 ± 22.7%; non-dyskinetic: 147.9 ± 18.6%) than in controls (170.8 ± 17.6%) and this was more evident in the dyskinetic patients ($P = 0.05$).

In the two groups of patients, levodopa had no significant effect on ICF (dyskinetic: 147.5 ± 19.5%; non-dyskinetic: 164.7 ± 21.4%).

3.2. Silent period

By increasing the stimulation intensity, the SP duration extended in all groups of subjects ($P < 0.0001$) (Supplementary Table 2). There were no differences in SP duration between controls, dyskinetic patients and non-dyskinetic patients,