Clinical Neurophysiology 123 (2012) 815–821

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Effects of theta burst stimulation on motor cortex excitability in Parkinson's disease

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See Editorial, pages 640–641

ARTICLE INFO

Article history:
Available online 25 September 2011

Keywords:
Motor cortex
Parkinson's disease
Transcranial magnetic stimulation
Theta burst stimulation
Cortical inhibition

HIGHLIGHTS

- Intermittent theta burst stimulation in human increases motor cortical excitability likely via frequency dependent, homosynaptic long-term potentiation-like effects.
- Intermittent theta burst stimulation produces similar increase in motor evoked potential and changes in intracortical circuits in Parkinson's disease patients whether in the ON or OFF medication states compared to healthy controls.
- Frequency dependent homosynpatic long-term potentiation-like plasticity is relatively preserved in Parkinson's disease.

ABSTRACT

Objective: Long-term potentiation (LTP)-like plasticity induced by paired associative stimulation (PAS) is impaired in Parkinson's disease (PD). Intermittent theta burst stimulation (iTBS) is another rTMS protocol that produces LTP-like effects and increases cortical excitability but its effects are independent of afferent input. The aim of the present study was to examine the effects of iTBS on cortical excitability in PD.
Methods: iTBS was applied to the motor cortex in 10 healthy subjects and 12 PD patients ON and OFF dopaminergic medications. Motor evoked potential (MEP) before and for 60 min after iTBS were used to examine the changes in cortical excitability induced by iTBS. Paired-pulse TMS was used to test whether intracortical circuits, including short interval intracortical inhibition, intracortical facilitation, short and long latency afferent inhibition, were modulated by iTBS.
Results: After iTBS, the control, PD ON and OFF groups had similar increases in MEP amplitude compared to baseline over the course of 60 min. Changes in intracortical circuits induced by iTBS were also similar for the different groups.
Conclusions: iTBS produced similar effects on cortical excitability for PD patients and controls.
Significance: Spike-timing dependent heterosynaptic LTP-like plasticity induced by PAS may be more impaired in PD than frequency dependent homosynaptic LTP-like plasticity induced by iTBS.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex has been investigated as a non-invasive treatment in Parkinson's disease (PD). rTMS at frequencies between 5 and 25 Hz enhances cortical excitability (Pascual-Leone et al., 1994) and transiently improves motor function in PD after a single session and exert prolonged effects after multiple sessions (Gilio et al., 2002; Khedr et al., 2003, 2006; Lomarev et al., 2006; Wu et al., 2008). Two recent systematic reviews (Fregni et al., 2005; Elahi et al., 2009) concluded that high frequency (>1 Hz) rTMS that increases motor cortex excitability (Pascual-Leone et al., 1994, 1998; Lomarev et al., 2006) is associated with improvement in PD motor signs and may be a useful therapy in PD, while low frequency rTMS that decreased cortical excitability had no significant effect (Elahi et al., 2009). However, it should be noted that changes in cortical excitability do not always correlate with changes in motor function (Baumer et al., 2009).

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doi:10.1016/j.clinph.2011.07.051

Impaired cortical plasticity may represent an important pathophysiological feature of PD. Long-term potentiation (LTP) like plasticity tested with paired associative stimulation (PAS) was decreased in PD patients off medications and was restored by dopaminergic medications in non-dyskinetic patients (Morgante et al., 2006; Ueki et al., 2006). However, PAS involves pairing of peripheral nerve stimulation with TMS and the effects of nerve stimulation on cortical excitability are abnormal in PD (Sailer et al., 2003). Therefore, it is possible that impaired PAS effects in PD are in part due to abnormal effects of nerve stimulation on the cortex. Huang et al. (2005) described a form of rTMS known as theta burst stimulation (TBS), involving bursts of three pulses at 50 Hz repeated at 5 Hz. Intermittent administration of TBS (iTBS), modeled on LTP induction protocols in animal studies, was found to increase motor cortex excitability in healthy subjects (Huang et al., 2005). Pharmacological studies (Huang et al., 2007) suggest that the effects are likely related to LTP-like mechanisms. While both PAS and iTBS involve LTP-like mechanisms, there are important differences. Based on analogy with animal studies, it may be hypothesized that PAS induces spike-timing dependent plasticity (Zhang et al., 1998; Bi and Poo, 1998) that depends on synchronous activation from two different inputs to the same cell (Wolters et al., 2005), while TBS is a form of homeotopic plasticity that depends on intermittent high frequency activation of the same input (Raymond, 2007). A previous study found that a single session of iTBS or other rTMS protocols produced only small effects in addition to the effects of motor training in PD (Rothkegel et al., 2009). How cortical inhibitory and excitatory circuits in PD patients are modulated by iTBS has not been reported.

Single and paired TMS can be used to test cortical inhibitory and excitatory circuits in PD. Short interval intracortical inhibition (SICI) is likely mediated by gamma-aminobutyric acid type A receptors (Kujirai et al., 1993) and reduced resting SICI in PD (Ridding et al., 1995) may occur at certain stimulus intensities (MacKinnon et al., 2005). Afferent input can also inhibit the cortex; median nerve stimulation about 20 ms before motor cortex stimulation produces short latency afferent inhibition (SAI)(Delwaide and Olivier, 1990; Tokimura et al., 2000) while long latency afferent inhibition (LAI)(Chen et al., 1999) is produced at interstimulus intervals (ISIs) of about 200 ms. In PD patients, SAI is normal off medication but is reduced in the ON medication state, while LAI is reduced in both ON and OFF medications (Sailer et al., 2003).

In the present study, we examined the effects of iTBS on cortical excitability in PD patients ON and OFF medications. Our first objective was to examine LTP-like mechanisms elicited by iTBS in PD. Our second objective was to examine the impact of iTBS on several cortical circuits (SICI, ICF, SAI, LAI) previously found to be abnormal in PD. Since 5 Hz rTMS increases motor evoked potential (MEP) amplitude to a lesser degree in PD patients OFF medications compared to controls (Gilio et al., 2002) and LTP is one of the proposed mechanisms for the effects of high frequency rTMS (Rossi et al., 2009), our first hypothesis is that the LTP-like effects of iTBS will be reduced in PD patients OFF medications. Our second hypothesis is that the LTP-like effect of iTBS will be restored in the ON medication state, suggesting that the LTP-like effects of iTBS and PAS are affected in similar manner in PD (Morgante et al., 2006; Ueki et al., 2006).

2. Methods

2.1. Subjects

We studied 12 moderate PD patients (Table 1) and 10 age-matched healthy controls (6 women, aged 63.1 ± 8.8 years, range 50–75 years). Patients were recruited from the Movement Disorders Center at the Toronto Western Hospital. Exclusion criteria were significant tremor, cognitive impairment, disabling dyskinesia or taking antidepressants. Patients were studied after overnight withdrawal of dopaminergic medications (OFF session), and on dopaminergic medication (ON session) in random order on separate days at least one week apart. For the ON group, medications were taken at the regularly scheduled intervals and the experiments for the ON state began one to one and half hour after intake of dopaminergic medications when the patient noticed subjective improvement. The ON state was also confirmed by comparing motor Unified Parkinson's disease rating scale (UPDRS) III scores to clinical records. If necessary, an additional dose was given for wearing off symptoms. Parkinsonism was assessed with motor UPDRS and dyskinesia was assessed using items 32 and 33 of UPDRS-IV (Table 1). All subjects gave written informed consent. The protocol was approved by the University Health Network Research Ethics Board.

2.2. EMG recording

EMG from the first dorsal interosseous (FDI) muscle was amplified, filtered (20 Hz–2.5 kHz), digitized at 5 kHz and stored on a personal computer for off-line analysis. Subjects relaxed throughout the experimental session.

2.3. Somatosensory evoked potential

The median nerve stimulation (MNS) was applied at the wrist with a standard bar electrode with cathode positioned proximally. The stimuli were 200 μs constant current square wave pulses adjusted to produce a slight thumb twitch. Median nerve somatosensory evoked potentials (SEPs) were recorded with the active electrode at C3′or C4′ (2 cm posterior to C3 or C4) referenced to Fz. The N20 peak latencies were determined from the average of 200 trials. SEP was tested in the first study session for each patient.

2.4. Transcranial magnetic stimulation

TMS before and after iTBS was performed with a 7-cm figure-of-eight coil and two Magstim 200 stimulators connected via a Bistim module (The Magstim Company, Whitland, UK). The handle of the coil pointed backwards and laterally at about 45° from the midline. The optimal coil position for eliciting MEPs in the FDI muscle was determined. MEPs were recorded from the more affected arm unless tremor or dyskinesia made measurements difficult, in which case the less affected arm was studied (Patients 6 and 8, Table 1). The dominant or non-dominant sides studied in control subjects were randomly chosen and was identical to PD patients (5 each). The resting motor threshold (RMT) was the minimum stimulator intensity eliciting MEPs of >50 μV in 5 out of 10 consecutive trials (Rossini et al., 1994). Active motor threshold (AMT) was the minimum intensity needed to evoke MEPs of >100 μV in at least 5 out of 10 trials while maintaining 20% maximum contraction aided by audiovisual feedback of EMG activity. AMT was determined separately for the Magstim 200 and the Magstim Super Rapid stimulator. SICI was elicited using conditioning stimulus (CS) at 90% AMT followed by test stimulus (TS) at 2 ms ISI and ICF used 10 ms ISI. SAI was elicited using MNS at N20 + 3 ms and LAI used MNS 200 ms before TS.

2.5. Intermittent theta burst stimulation

iTBS was performed with a 7-cm air-cooled figure-of-eight coil connected to a Magstim Super Rapid stimulator, using the same handle orientation as in the previous section. TBS consists of 3 pulses at 50 Hz given at 5 Hz at 80% AMT. iTBS consists of a 2 s