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High frequency repetitive transcranial magnetic stimulation decreases cerebral vasomotor reactivity

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ABSTRACT

Objective: Repetitive Transcranial Magnetic Stimulation (rTMS) has been recently employed as a therapeutic strategy for stroke, although its effects on cerebral hemodynamics has been poorly investigated. This study aims to examine the impact of high frequency rTMS on cerebral vasomotor reactivity (VMR).
Methods: Twenty-nine healthy subjects were randomly assigned to real (19) or sham 17-Hz rTMS, applied on primary motor cortex (M1) of the dominant hemisphere. All subjects underwent Transcranial Doppler of the middle cerebral arteries to evaluate mean flow velocity and VMR before (T_0) and within 10 min (T_1) following rTMS. Four subjects underwent further VMR evaluations at 2 (T_2), 5 (T_3) and 24 h (T_4) after rTMS. As a control condition, 10 subjects underwent real (5) or sham rTMS on calcarine cortex. In addition, five acute stroke patients underwent five daily rTMS sessions on the affected hemisphere mimicking a therapeutic trial.
Results: Following real rTMS on M1 ($p = 0.002$) and calcarine cortex ($p < 0.001$) VMR decreased with respect to T_0 in both hemispheres, while no change was observed after sham rTMS ($p > 0.6$). VMR tended to remain lower than T_0 until T_3. Cerebral VMR decreased independently of the stimulated side also in the patients' group.
Conclusions: High frequency rTMS reduces cerebral VMR, possibly as a secondary effect on autonomic control of cerebral hemodynamics.
Significance: The effect of rTMS on cerebral hemodynamics should be carefully considered before proceeding toward a therapeutic application in stroke patients.

1. Introduction

Brain metabolism is tightly dependent on an adequate oxygen and glucose blood supply. Therefore, the brain needs a rapid adaptation of blood flow to local changes of metabolic demands, and a nearly constant perfusion under different physiological and/or pathological conditions (Kuschinsky and Wahl, 1978).

Distinctively from other vascular systems, cerebral circulation has anatomical and functional mechanisms that allow to prevent hypoperfusion. In particular, cerebral hemodynamics is characterized by two peculiar properties: autoregulation, i.e. the capability to maintain a constant perfusion in a wide systemic blood pressure (BP) range, and vasomotor reactivity (VMR), i.e. the potential of cerebral vessels to dilate following hypercapnia. Three control systems orchestrate these properties: the myogenic, the metabolic and the autonomic (Edvinsson et al., 1976). Clinical data demonstrated that these control systems are essential in reducing ischemia-related brain damage (Eames et al., 2002). Prospective studies showed that either an impaired cerebral VMR or an altered autoregulation are an independent risk factor for stroke occurrence in patients with carotid artery disease (Vernieri et al., 1999; Markus and Cullinane, 2001; Reinhard et al., 2008).

High frequency repetitive transcranial magnetic stimulation (rTMS) applied over the motor cortex of the affected hemisphere was recently proposed as a possible treatment facilitating recovery from stroke (Khedr et al., 2005; Kim et al., 2006). However, these pioneering observations lack prolonged follow-up studies (Rossini and Johnston, 2005; Ziemann, 2005).

High frequency rTMS was reported to increase cerebral blood flow (CBF) velocity (Pecuch et al., 2000; Speer et al., 2000; Takano et al., 2004) in the stimulated area of healthy subjects. However, this effect was challenged by other studies (Paus et al., 1998).

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Moreover, the impact of rTMS on cerebral VMR has never been investigated. This study aimed to examine the effects of high frequency rTMS on cerebral VMR in a sample of healthy subjects and acute stroke patients.

2. Methods

2.1. Subjects

Thirty healthy subjects were selected for the study. To estimate the risk of seizures, we performed an electroencephalogram (EEG) and took detailed personal and family histories. A color-coded duplex of the neck vessels (iU22, Philips Ultrasound, Bothell, WA, USA) and a transcranial Doppler (TCD, Multidop X Digital, DWL, Sipplingen, Germany) were carried out to exclude any stenosis that could determine a compensatory dilatation in the distal circulation, with a consequent reduction of VMR (Vernieri et al., 2004; Reinhard et al., 2005).

Eligibility criteria for rTMS were defined according to the recommendations of the International Federation of Clinical Neurophysiology (IFCN) (Rossini et al., 1994; Wassermann, 1998).

Among the 30 screened volunteers, 29 healthy subjects (19 female, 22–45 years) were enrolled and underwent the study protocol. Only one subject was excluded for febrile convulsion history.

In addition, five patients (1 female, 58–84 years) suffering from an acute ischemic stroke in the middle cerebral artery (MCA) territory were enrolled in the study. Stroke was diagnosed by brain CT or MR scan at admission and clinical status was assessed by NIH stroke scale (NIHSS).

2.2. Repetitive TMS

Real rTMS was applied on the primary motor (M1) cortex, with a figure-of-eight coil connected with Magstim Super Rapid R magnetic stimulator (MagStimCo. Ltd., Whitland, Dyfed, UK). The flat surface of the coil was held tangentially to the scalp, at 45° respect to sagittal plane. The "hot spot" and the rest Motor Threshold (MT) of the first dorsal interosseus (FDI) were defined according to the IFCN recommendations, using surface EMG monitoring (Rossini et al., 1994). Stimulus intensity was increased by 10% of the MT. Subjects seated on a reclining armchair with pronated hands, in a soundproof room, without visual access to the equipment display. rTMS consisted of eight trains of 3 s at 17 Hz, with a rest period of 5 min in between (408 pulses in total). The 17 Hz frequency has been already employed in 'therapeutic' studies (i.e. drug-resistant major depression, Miniussi et al., 2005) and was chosen for being within the frequency range with "facilitatory/excitatory" effects as previously tested by means of paired-pulse protocol (Kujirai et al., 1993). Repetitive TMS over the calcarine cortex was also performed according to Bohotin et al. (2002). The coil was placed in a vertical position (its handle upward) on the inion–nasion line with its inferior limit about 1 cm above the inion, and then shifted laterally to find the optimum point for phosphene induction. According to safety international recommendations for rTMS (Chen et al., 1997; Machii et al., 2006), the coil was placed on the phosphene detection spot and the stimulus intensity was set at the phosphene threshold; the other parameters were equal to the M1 rTMS. This was considered a 'control' condition to investigate the presence/absence of effects selectively linked to carotid artery territory or to a more widespread effect also extended to the vertebro-basilar district.

Both motor and calcarine sham sessions were performed using a sham coil in a position and with stimulation parameters equal to the real stimulation, except for an intensity reduction of 20% of the stimulator output, well below any physiological effect on the brain. We did this in order to keep unmodified the protocol setting conditions (i.e. a similar acoustic noise without electrical stimulation) even when sham stimulation was applied.

During both motor and calcarine stimulations, to stimulate on a constant site, an adherent, inelastic cap marked on the 'hot spot' was modelled on the head, with reference to nasion–inion and interaural lines.

2.3. Transcranial Doppler

Examination of vessels of the circle of Willis was performed by means of TCD as described by Aaslid et al. (1982). Cerebral VMR to hypercapnia was evaluated by means of CO_2 reactivity test. During the experiments, end-tidal expiratory CO_2 was measured by means of a capnometer (Drager Capnodig). Mean arterial blood pressure (mABP) was monitored by means of a BP monitor (2300 Finapress, Ohmeda). The study was carried out in a quiet room, with patients lying in a comfortable supine position, without any visual or auditory stimulation. Two TCD dual 2-MHz transducers fitted on a headband and placed on the temporal bone windows were used so as to obtain a bilateral continuous measurement of mean flow velocity (MFV) in the middle cerebral arteries (MCAs) insonated at a depth of 50 ± 4 mm. Once the signals recorded became stable, MFV and end-tidal CO_2 at rest were obtained through the continuous recording of a 60-second period of normal room air breathing. Hypercapnia was induced by the inhalation of a mixture of 7% CO_2/air, and subjects breathed through the mask until MCA flow velocity became stable. Once equilibrium was reached, a further 30-second recording was made at this stage (plateau period). The maximal vasodilatory range (Markus and Cullinane, 2001) was determined by the percentage increase in MCA velocity occurred during the administration of 7% CO_2 mixture.

Each experiment consisted of three consecutive periods, i.e. a 60-second rest period, the 90-second CO_2 inhalation period – always including for each subject the 30-second plateau period – and, finally, the 90-second recovery period. Each experiment described above was repeated at least three times, at 10-minute intervals at least. The MFV baseline value was taken as the average of the rest period (60 s). The MFV CO_2 value was the average of the plateau period of 30 s. VMR values were obtained according to the formula (Vernieri et al., 2004):

$$\mathrm{VMR} = \left[\frac{(\mathrm{MFV}_{\mathrm{CO2}} - \mathrm{MFV}_{\mathrm{Baseline}})}{\mathrm{MFV}_{\mathrm{Baseline}}}\right] \cdot 100$$

Data from the three experiments were averaged for each subject.

2.4. Study protocols

The 29 healthy subjects were randomized to real or sham motor rTMS according to a pseudo-casual randomization list, with a ratio real:sham of 2:1. Nineteen subjects (13 female; 26.5 years, SD = 2.4) were assigned to real rTMS, 10 (6 female, 25.1 years, SD = 1.4) to sham rTMS. In order to eliminate the possible influence produced by interindividual differences, six subjects underwent both real and sham stimulations in a randomized order, with at least one week interval in between. As a further control condition, occipital rTMS was carried out on ten subjects randomly assigned to real (5) or sham (5) rTMS. Healthy volunteers underwent a basal evaluation of MFV and VMR (T_0) measured in MCAs, a single session of real or sham rTMS and a second evaluation of MFV and VMR (T_1), within 10 min following the end of rTMS (Fig. 1). The procedures were double-blinded: both the subjects and the neurosonologists were unaware of the type of rTMS (real or sham). In addition, MFV and VMR were evaluated at T_2 (after 2 h from rTMS), T_3 (after 5 h) and at T_4 (after 24 h) in four healthy subjects