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Cyclical changes of cortical excitability and metaplasticity in migraine: Evidence from a repetitive transcranial magnetic stimulation study

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ABSTRACT

The primary brain dysfunctions leading to the onset of a migraine attack remain largely unknown. Other important open questions concern the mechanisms of initiation, continuation, and termination of migraine pain, and the changes in brain function underlying migraine transformation. Brief trains of high-frequency repetitive transcranial magnetic stimulation (rTMS), when applied to the primary motor cortex at suprathreshold intensity ($\geqslant$120% of resting motor threshold [RMT]), elicit in healthy subjects a progressive, glutamate-dependent facilitation of the motor evoked potentials (MEP). Conversely, in conditions of increased cortical excitability, the rTMS trains induce inhibitory MEP responses likely mediated by cortical homeostatic mechanisms. We enrolled 66 migraine-without-aura patients, 48 migraine-with-aura patients, 14 patients affected by chronic migraine (CM), and 20 healthy controls. We assessed motor cortical response to 5-Hz rTMS trains of 10 stimuli given at 120% RMT. Patients with episodic migraine were studied in different phases of the migraine cycle: interictal, preictal, ictal, and postictal states. Results showed a facilitatory MEP response during the trains in patients evaluated in the preictal phase, whereas inhibitory responses were observed during and after a migraine attack, as well as in CM patients. In the interictal phase, different responses were observed, depending on attack frequency: facilitation in patients with low and inhibition in those with high attack recurrence. Our findings suggest that changes in cortical excitability and fluctuations in the threshold for inhibitory metaplasticity underlie the migraine attack recurrence, and could be involved in the process of migraine transformation.

1. Introduction

Migraine is a neurological disorder with complex and poorly understood underlying mechanisms. Most current models of migraine pathogenesis claim that a condition of brain hyperresponsivity to several exogenous and endogenous stimuli may underlie the susceptibility to migraine attacks [8,23,50,62]. However, the exact pathophysiological mechanisms leading to the attack onset remain under debate. Some authors have pointed to the brainstem as "the generator" of the attacks [1,18,61], whilst others have provided evidence that the migraine attacks may start at the cortical level [15,50,63].

The process of migraine "transformation" has become another hot topic of research in the field of migraine pathophysiology. It refers to the progression over time from episodic migraine (EM) to chronic migraine (CM), a condition associated with more severe disability and possibly higher risk of brain damage [12,14,53]. Though many risk factors, such as obesity and medication overuse, have been identified, the mechanisms of disease evolution are still unknown [11].

In recent decades, transcranial magnetic stimulation (TMS) has evolved as an excellent tool to noninvasively investigate the cortical excitability state in vivo in various neurologic disorders [52]. Very few studies, however, have been performed in EM patients in different phases of the migraine cycle, and conflicting findings have been reported in CM patients.

Aims of the present work were: 1) to investigate changes in motor cortical excitability throughout the migraine cycle (ie, interictal, preictal, ictal, and postictal periods) in patients suffering from episodic migraine with (MwA) and without aura (MwoA); 2) to

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compare motor cortical excitability among EM and CM patients, and healthy subjects; 3) to evaluate whether different patterns of cortical excitability underlie different clinical phenotypes.

The TMS paradigm used in the study consists of brief trains of repetitive TMS (rTMS) applied over the hand primary motor cortex at 5-Hz frequency and intensity of 120% of resting motor threshold (RMT). In normal subjects, the rTMS trains induce a progressive potentiation of the motor evoked potentials (MEPs) elicited at each train stimulus [48] that is thought to be mediated by presynaptic facilitatory mechanisms of glutamate release [30,37]. The presynaptic glutamatergic terminal also represents a crucial site for the homeostatic regulation of cortical excitability, that is, cortical homeostatic plasticity, or metaplasticity [43,46,47]. Accordingly, 5-Hz rTMS trains given at 120% RMT have been shown to induce, in condition of experimentally enhanced cortical activity, inhibitory homeostatic MEP responses in normal subjects [26].

On these bases, in the present work, 5-Hz rTMS trains were applied at 120% RMT to the migraine motor cortex to focus on the interplay between abnormal cortical excitability and mechanisms of cortical metaplasticity in different migraine subtypes. Metaplasticity refers to those mechanisms that stabilize cortical excitability by keeping neuronal firing rates within a physiological dynamic range [10,58]. Recently, it has been suggested that metaplasticity could play a role in migraine pathogenesis [4,25,57].

Our study might provide useful clues as to how changes in cortical excitability and homeostatic plasticity could contribute to the paroxysmal nature of migraine and its tendency to evolve over time.

2. Methods

2.1. Subjects

One hundred forty-eight right-handed subjects were eligible to participate in this study: 66 patients with MwoA (51 F/15 M, mean age 37.9 ± 9.6 years), 48 patients with MwA (34 F/14 M, mean age 38.3 ± 12.4 years), 14 patients with CM (12 F/2 M, mean age 38.3 ± 14.5 years), and 20 healthy controls (15 F/5 M, mean age 33.8 ± 7.5 years) without past medical history or familiarity for migraine. Patients were recruited from the Headache Outpatient Service of the Neurology Department at the University of Palermo, Italy.

Diagnoses of EM and CM were made according to the International Classification of Headache Disorders, 2nd edition [21] and the revised criteria [35], respectively. Additionally, a daily headache diary was used to assess headache characteristics for a minimum of 3 months before the patients were enrolled in the study. All patients suffering with MwA experienced visual aura in at least 50% of their attacks. EM patients with or without aura had a mean attacks frequency ranging from 0.5 to 8 attacks per month (1–12 headache days), while CM patients had monthly migraine days $\geqslant$ 8 and headache days $\geqslant$ 15 for at least 3 months. All CM patients had past history of MwoA meeting International Headache Society criteria. None of the participants was taking prophylactic drugs at least 3 months prior to the study. CM patients were excluded if their headaches followed head trauma, if they had a prominent psychological illness, or if their headaches occurred in the presence of symptomatic medication overuse. All patients denied any history of systemic or other neurological diseases, and presented normal physical and neurological examinations.

Different subgroups of patients with EM were evaluated in different phases of the migraine cycle. The subjects who did not have migrainous headache within a period of 2 days before and after the experimental evaluation were classified as interictal. Patients suffering from a migraine attack at the time of the experiment were classified as ictal, whereas those evaluated within the 48 hours preceding or following the headache were respectively classified as preictal and postictal. Based on previous work [19], recordings for CM patients were performed as in interictal EM patients (no acute migraine within the 48 hours preceding or following the electrophysiological evaluation) but present background (or interval) headache during evaluation was allowed. Occurrence of attack after recording was verified by means of a telephone call. Selection of the time window for the peri-ictal period was based on earlier studies [31,40].

To avoid possible unspecific effects related to pharmacological activity, patients underwent the electrophysiological assessment only when they had not taken symptomatic medications in the 24 hours preceding the evaluation. To minimize any hormonal effect, female patients and controls were not examined during the menstrual phase.

Before enrollment, all the subjects were checked for contraindications to TMS [41], and gave their written informed consent to participate. The study conformed to the Declaration of Helsinki, and the experimental procedures were approved by the local ethics committee. The demographic and clinical data of subjects are summarized in Table 1.

2.2. Stimulation procedures

All subjects were comfortably seated on a chair and told to be as relaxed as possible. They wore a tight-fitting plastic swimming cap to mark the optimum stimulation site and ensure optimum coil placement. Electromyography (EMG) signals were recorded from the right abductor pollicis brevis muscle using 0.9-cm-diameter Ag–AgCl surface electrodes placed 3 cm apart over the belly and tendon of the muscle. The EMG activity was recorded with a bandpass of 10 to 1000 Hz and a display gain ranging from 50 to 1000 μV/cm. EMG signals were collected, averaged, and analyzed off-line. Focal TMS was delivered over the hand motor cortex of the left hemisphere using a figure-of-8 coil connected to a monophasic Cadwell High Speed Magnetic Stimulator (Cadwell Laboratories, Kennewick, WA, USA). The stimulating coil with posteroanterior orientation was placed over the optimal site for eliciting responses in the contralateral target muscle [3]. The RMT for eliciting responses in the relaxed abductor pollicis brevis muscle was defined as the minimum intensity of stimulation needed to produce responses of 50 μV in at least 50% of 10 trials. The subjects were given audiovisual feedback of EMG activity to help maintain complete muscle relaxation. The coil position was continuously monitored throughout the experiment in order to keep it constant. Stimulation was performed following safety guidelines [51].

2.3. Experimental paradigm and measurements

All subjects underwent an experimental evaluation consisting of 6 trains of 10 stimuli delivered at 5-Hz frequency to the left primary motor hand area. The rTMS trains were applied with a 2-minute intertrain interval on subjects at rest at an intensity of the stimulator output equal to 120% of the RMT. To evaluate changes in MEP size during the rTMS trains, for each subject, MEP amplitudes were calculated peak-to-peak from single traces and then averaged according to their position in the train. In addition, since different, even opposite (facilitatory or inhibitory) MEP responses may be elicited by the rTMS trains [16,25,26], individual analyses were made and the response pattern in each subject was classified as "facilitatory," "inhibitory," or "flat." We classified as "facilitatory" the responses in which at least 6 of the MEPs following the first in the train were larger in amplitude as compared to the first MEP, with a ratio between the largest and the first MEP size $\geqslant$ 1.3.