Influence of stimulation intensity on intracortical facilitation in migraine with and without aura

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Background

Recently, it has been supposed that different methods of testing brain excitability could shed light on different pathophysiological aspects of the so-called migraine cortical "disexcitability", as they can induce different degrees of cortical activation (*Cosentino et al., 2013*).

The paired-pulse Transcranial Magnetic Stimulation (ppTMS) paradigm allows to evaluate intracortical inhibition and facilitation of the motor circuits (*Ziemann et al., 1996; Hallett, 2007*). In such studies, a conditioning stimulus modulates the amplitude of the MEP produced by the test stimulus. At intervals between 8 and 30 ms there is facilitation (intracortical facilitation, ICF), that is thought to be mediated by the glutamatergic intracortical circuits. Siniatchkin et al. (2007) found a more pronounced ICF in patients suffering from migraine as compared with healthy controls, whilst others (*Afra et al., 1998; Werhahn et al., 2000*) failed to find such a difference. We hypothesize that differences in the stimulation intensity used in these studies to apply the conditioning and/or test pulse could explain these discrepancies.

Aim of this study was to evaluate to which extent intracortical facilitation vary in relation to the intensity of the "test stimulus" in migraine patients as compared to the healthy subjects.

Materials and methods

Fourteen patients suffering from migraine with (n=7) and without (n=7) aura and 10 healthy subjects were enrolled in the study. In each subject we assessed ICF by using a paired-pulse paradigm with ISI of 10 ms, intensity of the conditioning stimulus (CS) equal to 80% of the resting motor threshold (RMT) and intensity of the test stimulus (TS) ranging between 100% and 150% of the RMT in steps of 10%. Electromyographic (EMG) responses to paired-pulse transcranial magnetic stimulation (TMS) were recorded from the relaxed abductor pollicis brevis (APB) muscle. Two-way repeated-measures analyses of variance (ANOVAs) were performed. Conditioned MEP/ Unconditioned MEP ratio were computed in each subject and used for the statistical analyses. Duncan post hoc test was used for multiple comparisons of means. For all analyses the statistical significance was set at p values lower than 0.05.

Results

ANOVA showed a significant interaction between factors "intensity of stimulation" (6 intensity levels) and "group" (migraine and healthy subjects) ($p<0.00001$). At the post hoc analyses we observed a significant difference in the mean conditioned MEP (cMEP) / unconditioned MEP (MEP) ratio between patients and controls only at intensities of 100% and 110% ($p<0.05$) of the TS (Fig.1, 2). Statistical analyses also showed that a significant facilitation of MEP responses was achieved at intensities of the TS equal or up to 120% ($p<0.05$) in the healthy controls. Conversely, in migraineurs a significant facilitation was observed only at 100% ($p=0.01$) and 110% ($p=0.02$) intensities (Fig. 3).

No significant differences were observed between patients affected by migraine with and without aura.

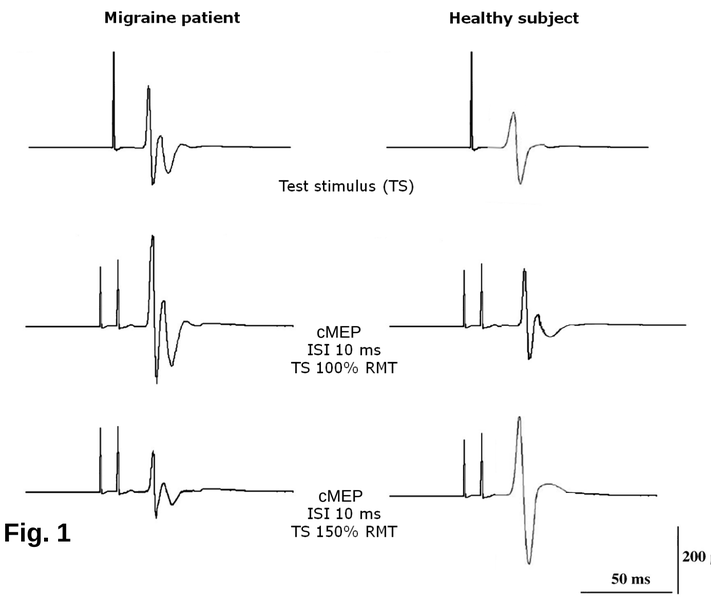

Fig. 1

Fig. 1. Representative examples of intracortical facilitation (ICF) at intensities of 100% and 150% of the test stimulus (TS) in a patient with migraine and in an healthy subject. Note that a MEP potentiation is observed in the patient at 100% but not a 150%. Conversely, in the normal subject a MEP potentiation is achieved when using 150% but not 100% intensity of TS.

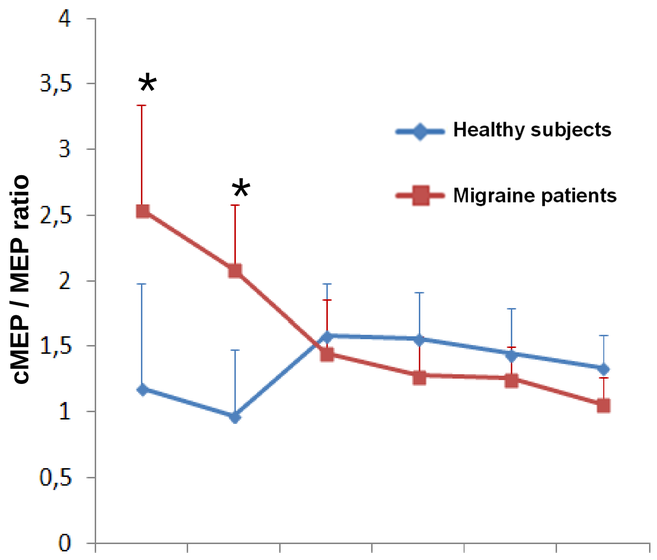

Fig. 2

Fig. 2. Mean conditioned/unconditioned MEP ratios in migraineurs and control subjects at different intensities of the test stimulus (TS). * indicate significant differences between migraineurs and controls ($p<0.05$).

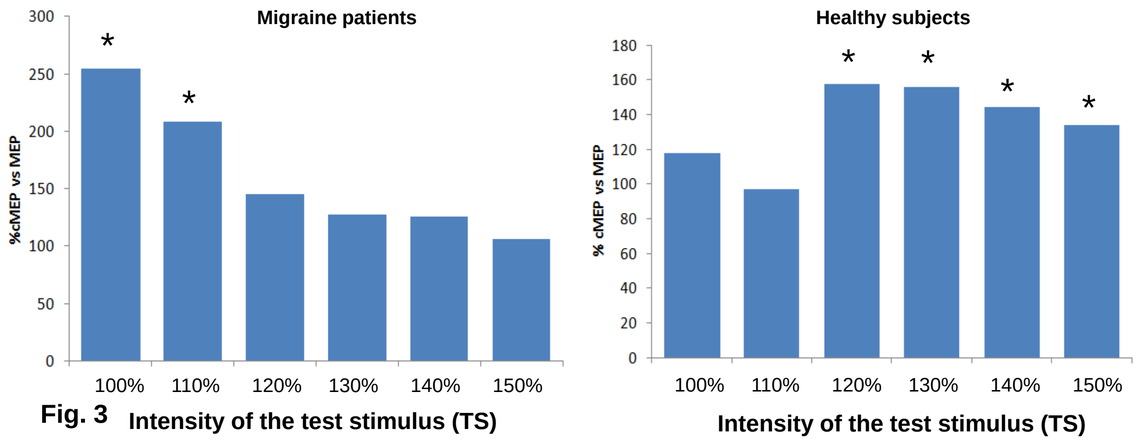

Fig. 3

Fig. 3. Mean conditioned MEP (cMEP) amplitudes expressed as a percentage of the unconditioned MEP (MEP) in migraineurs and control subjects. * indicate significant differences between mean conditioned MEP and unconditioned MEP amplitude ($p<0.05$).

Conclusions

In migraine, hyperresponsivity of the facilitatory intracortical circuits may be detected by means of the paired-pulse TMS (with interstimulus intervals of 10 ms) only when using a low intensity of the TS, that is unable to induce significant MEP facilitation in normal subjects. At higher stimulation intensities of the TS, we did not find any significant MEP potentiation in migraine. These could be consequence of inhibitory compensatory mechanisms of cortical excitability elicited by a high-magnitude stimulation in a condition of basal cortical hyperexcitability. Possible mechanisms involved could be: 1) Feedback activation of the GABAergic intracortical circuits; 2) Activation of inhibitory homeostatic mechanisms of glutamate release in the presynaptic terminal.

In conclusion, our results support the hypothesis that different pathophysiological mechanisms may coexist in migraine, being possibly either expression of increased cortical responsivity or compensatory mechanisms seeking to stabilize the cortical excitability level.

References

•Afra J, Mascia A, Gérard P, et al. Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. Ann Neurol. 1998b; 44(2):209-15.
•Cosentino G, Fierro B, Brighina F. From different neurophysiological methods to conflicting pathophysiological views in migraine: a critical review of literature. Clin Neurophysiol. 2014 Sep;125(9):1721-30.
•Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007; 19;55(2):187-99.
•Siniatchkin M, Kröner-Herwig B, Kocabiyik E, Rothenberger A. Intracortical inhibition and facilitation in migraine-a transcranial magnetic stimulation study. Headache. 2007; 47(3):364-70.
•Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol. 1996; 496 (Pt 3):873-81.
•Werhahn KJ, Wiseman K, Herzog J, et al. Motor cortex excitability in patients with migraine with aura and hemiplegic migraine. Cephalalgia. 2000; 20(1):45-50.

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