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Transcranial Magnetic Stimulation Reveals Cortical Hyperexcitability in Episodic Cluster Headache

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Abstract: Evidence shows involvement of the cerebral cortex in the pathophysiology of cluster headache (CH). Here we investigated cortical excitability in episodic CH patients by using transcranial magnetic stimulation. In 25 patients with episodic CH and 13 healthy subjects we evaluated the motor cortical response to single-pulse (ie, motor threshold, input-output curves, cortical silent period) and paired-pulse (ie, intracortical facilitation, short intracortical inhibition) transcranial magnetic stimulation in both hemispheres. Thirteen patients were evaluated outside bout and the remaining 12 patients inside bout. Our results showed increased slope of the input-output curves after stimulation of both hemispheres in patients outside bout and in the hemisphere contralateral to the headache side in patients inside bout. Increased intracortical facilitation was observed in the hemisphere ipsilateral to the headache side in patients evaluated both outside and inside bout; reduced short intracortical inhibition was observed in patients inside bout ipsilateral to the side of pain. In conclusion, we provide evidence of increased cortical excitability in episodic CH both outside and inside bout, especially in the hemisphere ipsilateral to the side of headache attacks. Our results suggest that an abnormal regulation of cortical excitability could be involved in the pathophysiology of CH.

***Perspectives:** We investigated cortical excitability in episodic cluster headache by using transcranial magnetic stimulation, providing evidence of cortical hyperexcitability in patients both inside and outside bout. We suggest that an abnormal state of cortical excitability could be involved in the pathophysiology of the disease.*

***Key words:** Episodic cluster headache, pathophysiology, transcranial magnetic stimulation, cortical excitability, motor cortex.*

Cluster headache (CH) is an extremely painful headache disease, clinically impressing with strictly unilateral pain accompanied by ipsilateral cranial autonomic symptoms. The headache attacks typically occur in cluster periods lasting several weeks or months (inside bout), separated by remission periods of months or years (outside bout). The pathophysiology of CH is not comprehensively understood, being still indistinct as to how different peripheral and central neural mechanisms reciprocally interact to determine the clinical features of the disease. Modern techniques of functional neuroimaging have supported the hypothesis that some peculiar features of CH might rely on the hypothalamus involvement.[23,24,36] A hypothalamic dysfunction could also account for the abnormal central disinhibition of the trigeminal nociceptive system as evidenced by most electrophysiological studies in CH. [27,31] Indeed, as the hypothalamus plays a central role in modulating the trigeminal-autonomic reflex,[5,25] it is conceivable that its dysfunction could result in a destabilization of the balance between pronociceptive and antinociceptive inputs acting on the trigeminovascular system. However, it is still debated whether the hypothalamus actively contributes to the generation of the attacks, or whether its activation occurs just after the attack onset, in the context of a larger "pain matrix," for modulating CH. Consistent with this latter hypothesis, there is experimental evidence that brain areas involved in processing of pain stimuli are extensively activated during cluster attacks, but not in pain-free states.[24,36,38]

Therefore, if on the one hand the hypothalamic impairment could affect activity of several brain areas,[37] on the other it has been supposed that in CH a hypothalamic dysfunction could be orchestrated by

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many other brain regions, including the brainstem nuclei, the thalamus, and the cerebral cortex.[1,2,38] Neurophysiological studies of visually, somatosensory, and auditory evoked potentials have provided evidence of impaired cortical information processing in CH.[9,16,39] The cerebral cortex involvement is also supported by the occurrence of aura symptoms in CH patients as reported by different authors; indeed, the cortex is most likely the source of the aura symptoms.[4,30,33] In spite of the above, a very limited amount of research has been performed to investigate the contribution of the cerebral cortex in the pathogenesis of CH.

Transcranial magnetic stimulation (TMS) has been widely employed to noninvasively evaluate the cortical excitability state in migraine, and numerous TMS studies have given support to the concept that abnormal regulation of cortical excitability plays a pivotal role in the susceptibility and recurrence of the migraine attacks.[8,12] Instead, to our knowledge, no TMS studies have been conducted in CH until now. Thus, the aim of the present study was to investigate the excitability of the cerebral cortex in CH by using TMS. We assessed corticomotor excitability because different TMS paradigms can provide objective measures of activity and function of specific intracortical circuits in the human motor cortex.

Methods

Subjects

Twenty-five episodic CH patients (21 males, mean age 37.7 ± 10.5 years) and 13 sex- and age-matched healthy volunteers (HVs) without past medical history or familiarity for recurrent headache (11 males, mean age 35.2 ± 11.2 years) were enrolled in the study (Table 1). Diagnosis of episodic CH was made according to the International Classification of Headache Disorders (3rd edition, beta version).[19] All patients experienced strictly unilateral pain (16 right side, 9 left side). Exclusion criteria included coexistence of other primary or secondary headaches, family history of migraine, serious systemic or neurologic disease, or psychiatric disorder. Neurologic examination and brain magnetic resonance imaging were normal in all patients. Thirteen patients were studied outside bout (30–150 days after the end of the bout), whereas the remaining 12 patients underwent the experimental procedures inside bout, outside attacks (2–36 hours after the end of an attack). None of the patients was taking prophylactic drugs or corticosteroids at least 3 months prior to the study. Patients inside bout underwent the electrophysiological assessment only when they had not taken symptomatic medications in the 12 hours preceding the evaluation. To minimize any hormonal effect, female patients and controls were not examined during the menstrual phase.[35] Before enrollment, all the subjects were checked for contraindications to TMS[20] 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.

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. Electromyography (EMG) signals were recorded from the abductor pollicis brevis muscle using .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 1,000 Hz and a display gain ranging from 50 to 1,000 μV/cm. EMG signals were collected, averaged, and analyzed off-line. Focal TMS was applied over the hand motor cortex by using a figure-of-8 coil (double-circular 70-mm coil) connected to 2 Magstim 200 stimulators through a Bistim module (Magstim Co, Dyfed, UK). The stimulating coil was placed over the optimal site for eliciting responses in the contralateral target muscle. Excitability of the 2 hemispheres was investigated separately. The resting motor threshold (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. Stimulation was performed following safety guidelines.[29]

Experimental Paradigm and Measurements

All subjects underwent an experimental evaluation in which we assessed, in the hand motor cortex of both hemispheres, 3 measurements of cortical excitability. The first measurement was intracortical facilitation (ICF) and short intracortical inhibition (SICI). These measures were assessed by means of a paired-pulse paradigm

Table 1. Demographic and Clinical Characteristics and RMT Values of the Enrolled Subjects

Subject	Age, Y (Mean ± SD)	Gender, F/M (n)	Disease Duration, Y (Mean ± SD)	RMT Left Side/Headache Side (Mean ± SD)	RMT Right Side/Nonheadache Side (Mean ± SD)
HVs (n = 13)	35.2 ± 11.2	3/10	—	49.1 ± 4.1	48.1 ± 4.6
CH patients					
Outside bout (n = 13)	37.4 ± 11.2	2/11	11.4 ± 6.6	50.1 ± 9.3	49.6 ± 8.1
Inside bout (n = 12)	38 ± 10.8	2/10	14.2 ± 11.7	48.2 ± 9.2	48.5 ± 6.8

Abbreviations: SD, standard deviation; F/M, female/male.