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Lack of habituation of nociceptive evoked responses and pain sensitivity during migraine attack

Marina de Tommaso*, Luciana Lo sito, Olimpia Di fruscolo, Michele Sardaro, Maria Pia Prudenzano, Paolo Lamberti, Paolo Livrea

Neurologic and Psychiatric Sciences Department, Bari University, Clinica Neurologica, Policlinico, Piazza Giulio Cesare 11, 70124 Bari

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Abstract

Objective: The aim of the present study was to investigate the habituation of subjective pain sensation to CO_2 laser stimulus, in relation to the amplitude modifications of the cortical evoked responses (LEPs), during both the migraine attack and the not symptomatic phase.

Methods: Fourteen migraine patients were selected and compared with 10 healthy controls. Eight patients were evaluated during both the pain-free and the attack phases. Three following series of 20 averaged LEPs were recorded, stimulating the hands and the supraorbital zones: during the attack, two consecutive series of 20 averaged LEPs were carried out. The subjective sensation was requested for each laser stimulus, using a 0–10 points Verbal Rating Scale (VRS).

Results: In normal subjects the N2–P2 waves amplitude showed habituation across the three repetitions, which correlated with the habituation of the subjective rating of the stimulus. During the not symptomatic phase, patients showed a lack of habituation of the N2–P2 amplitude when the hand and the face was stimulated, with a pattern of increase of the pain rating across the three repetitions; in addition there was a lack of correlation between the LEPs amplitude and the subjective sensation. During the attack, the LEPs amplitude and the pain rating were increased when the face was stimulated, but they did not habituate across the two repetitions, likely the pain-free condition. The percent LEPs amplitude variation across the three repetitions correlated with the main indices of migraine severity, mainly when the supraorbital zone was stimulated.

Conclusions: The abnormal cortical excitability in migraine could condition an anomalous behavior of nociceptive cortex during the interictal phase of migraine: it persists during the acute phase, and correlates with the frequency and duration of migraine.

Significance: The reduced habituation of the nociceptive cortex may concur with the onset and evolution of headache.

Keywords: Laser evoked potentials; Pain rating; Habituation; Migraine

1. Introduction

The evoked potentials amplitude is a quantitative index of the neuronal population activated by certain sensory inputs; it tends to decrease during repetitive sensory stimulation, as the expression of a progressive reduction of the neuronal response. The physiologic phenomenon of a sensory cortex, which progressively reduces its activity in being reached by repetitive stimuli is known as habituation. According to the definition by Thompson and Spencer (1996), the habituation is a phenomenon of decrement in the amplitude of sensory cortical responses to repeated presentations of similar stimuli, excluding receptor or effector fatigue, in order to avoid brain over-stimulation.

Habituation has been found in experimental pain research. In fact subjects showed habituation to phasic noxious stimuli for different response systems (Bromm, 1980; Miltner et al., 1987; Kazarians et al., 1995).

Clinical neurophysiological studies have shown that laser (infrared CO_2, argon or thulium-YAG laser) can be used to generate an evoked potential that can be recorded from the vertex (late components) and temporal regions

* Corresponding author. Tel.: +39 80 5478546/539; fax: +39 80 5478532.
E-mail address: m.detommaso@neurol.uniba (M. de Tommaso).

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(early components) of the skull by selective activation of Aδ fibres (laser evoked potentials: LEPs) or C fibers (ultra-late laser evoked potentials) (Treede et al., 2003). The LEPs amplitudes correlate better with subjective pain ratings than with stimulus intensity (Bromm and Treede, 1991; Carmon et al., 1980), so it is general opinion that LEPs reflect neural processing of pain perception rather than stimulus encoding.(Treede et al., 2003). The amplitudes of LEPs tend to decrease with the repetitive stimulation, for the habituation effect.(Arendt-Nielsen, 1990; Kazarians et al., 1995; Valeriani et al., 2003; Weiss et al., 1997), but despite the close correlation between the LEPs amplitude and the pain sensation, they may be dissociated during repetitive stimulation, depending upon some factors as stimulus frequency (Treede et al., 2003).

The majority of evoked and event-related potentials studies in migraine have shown two abnormalities: increased amplitudes of averages of large numbers of trials and lack of habituation in successive trial blocks during the pain-free phase, with the ictal normalization of evoked potential amplitudes and habituation (Ambrosini et al., 2003). This pattern has suggested an abnormal state of cortical excitability during the interictal phase of migraine, which reversed during the attack for an homeostatic mechanism.(Ambrosini et al., 2003). A reduced habituation pattern of the LEPs in response to repetitive noxious stimuli was found during the interictal phase of migraine, in respect with control subjects, according to the results obtained by the application of other event-related potentials (Valeriani et al., 2003). The reduced habituation pattern seemed to involve mainly the vertex complex (Valeriani et al., 2003). In that study, we did not evaluate the behavior of the subjective pain rating across the repetitive laser stimulations. Further, during migraine attack patients showed an increase of LEPs amplitude (de Tommaso et al., 2002, 2004), which may suggest that the acute reversion of the electrophysiological abnormalities observed in migraine during the headache-free phase, should not involve the nociceptive system.

The mechanisms of pain processing and modulation seem fundamental in migraine pathogenesis (Welch, 2003): in this view, the aim of the present study was to further clarify the behavior of the subjective pain sensation during repetitive painful stimulations by CO_2 laser, in relation to the amplitude modifications of the cortical evoked responses, during both the migraine attack and the not symptomatic phase. We employed a three channels montage to detect only the vertex complex of the LEPs, in order to reduce the stress of the examination, which may provoke or worsen headache in migraine patients.

2. Methods

Subjects: fourteen patients suffering from migraine without aura, diagnosed according to the International Headache Society criteria (2004), were selected. They were all females, aged 18–40. All patients were diagnosed after six months' follow-up. Patients with general medical, neurological, or psychiatric diseases, and patients who were taking psycho-active drugs, or prophylactic treatment for headache, or who were assessed as overusing analgesic drugs in the last two months, were excluded from the study. Both the severity of headache, measured by the MIDAS scale (D'Amico et al., 2001), and the frequency of headache, measured in days with headache/month, were computed in the last six months.

All patients were evaluated at least 72 h after the end of the critical migraine phase (mean 75 + 2.1 h) and well before the next attack (mean 48 + 8.2 h), verified by the headache diary during a following clinical examination. In addition, in eight migraine patients the recording session was performed over a range of 4–6 h from the onset of the attack. The patients were instructed to attend a recording session at the onset of a migraine attack without taking triptans or other symptomatic drugs. They were examined by a neurologist with experience in headache and selected for the experimental task. The severity of headache was checked on a scale from 0 (no headache) to 3 (severe headache) (International Headache Society Committee on Clinical Trials in Migraine Guidelines for controlled trials of drugs in migraine, 1991).

Ten healthy subjects, with no concomitant general, neurological or psychiatric disease, served as controls: they were all females, aged 22–36. The experiments was undertaken with the understanding and written consent of each subject and with the approval of the local ethics committee of the Neurological and Psychiatric Department of Bari University.

The main clinical features of the patients and controls are summarized in Table 1.

2.1. CO_2 laser recording

The subject was seated in a comfortable chair, awake and relaxed with eyes closed in a quiet room kept at 21–23 °C. Both the subjects and experimenters wore protective goggles during data acquisition. All subjects underwent a recording session with three scalp electrodes placed along the midline (Fz, Cz, and Pz positions of the 10–20 International System) (impedance below 5000 ohms), referring to the nasion with the ground at Fpz.; another electrode was placed above the right eye to record the EOG. Signals were amplified, filtered (0.5–100 Hz), and stored on a biopotential analyzer (MICROMED System Plus; MICROMED, Mogliano Veneto, Italy; www.micromed-it.com). Time analysis was of 1000 ms, at a sampling rate of 2048 Hz. An automatic artifact rejection algorithm excluded from the average all runs containing transients exceeding 65 μV at each recording channel.