Are CO₂ laser evoked potentials a specific marker of migraine?

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Summary

Although neurophysiological studies have made a considerable contribution to understanding of migraine pathophysiology, the diagnosis of migraine continues to be based on clinical examination of the patient, which also includes careful history taking and a search for neurological signs. Indeed, no instrumental technique has ever disclosed specific features in migraineurs, able to distinguish them from healthy subjects or from patients with non-migraine headache. CO₂ laser evoked potentials (LEPs) have been used in migraine research in the past three years, proving very useful for demonstrating functional abnormalities of the central nociceptive system which might be linked to the pathophysiological mechanisms of this disease. However, like other neurophysiological methods, LEP recording in migraineurs has not revealed abnormalities specific enough to allow diagnosis of migraine in individual subjects.

KEY WORDS: human brain, laser evoked potentials, migraine.

The pathophysiology of migraine

In spite of the high prevalence of migraine in the general population and the extent of the functional impairment caused by the pain, which is its main symptom, the pathophysiological mechanisms of migraine are still not fully understood. This is basically because of the absence, in migraine, of any organic lesion (neuronal or otherwise). However, an increasing number of studies show functional abnormalities of the central nervous system (CNS) neurons, which result in altered cerebral cortex excitability (1). It has recently been clarified that migraine is primarily a disease of the nervous tissue, secondarily involving the vascular system (2-5). Since a migraine attack can potentially occur in any subject, there must be functional abnormalities, specific to migraine, able to perpetuate the migraine attack and thus to cause the “migraine disease”. They should be detectable in the headache-free period, since they differentiate migraine patients from healthy subjects and from patients with non-migraine headache. In migraine, reduced habituation to the afferent inputs during the interictal phase is one of the most characteristic neurophysiological features. Habituation is a physiological phenomenon in which sensory cortex activity decreases in response to repetitive stimuli. In habituation, the evoked potential (EP) amplitude, which is a quantitative index of the neuronal population activated by certain sensory inputs, tends to decrease during repetitive sensory stimulation, expressing a progressive reduction of the neuronal response. Increases and decreases in habituation, to pathological levels, may be due to changes in cortical excitability. In migraine, experiments designed to investigate EP modification after repetitive stimulation have demonstrated a lack of habituation (6-9). Since habituation has a protective purpose – to prevent the progressive accumulation of possibly toxic substances at cortical level – its reduction in migraine might represent the background to the development of the migraine attack (10). Indeed, the accumulation of lactate and protons, if not countered by neuronal habituation, might lead to an imbalance of the metabolic homeostasis, and thus to activation of the trigeminovascular system (10).

Another biological mechanism thought to play a primary role in the pathophysiology of the migraine attack, known as sensitization, is an increased response of neurons in the CNS to afferent inputs. The presence of cutaneous hyperalgesia and allodynia in the trigeminal territory during spontaneous migraine pain may be due to CNS sensitization (11).

Functional assessment of the central nervous system in migraine: CO₂ laser evoked potentials

The increasing evidence that migraine involves, primarily, the cerebral neurons and that the trigeminovascular system is only a peripheral effector of a pathological cascade that arises within the brain has emphasized the need to focus scientific investigation on the CNS. The CNS morphology is obviously normal in migraineurs, who do not have any lesion of the motor, sensory or cognitive brain areas. Hyperintense lesions in T2 MR images are sometimes evident in migraine patients, but their meaning in migraine pathophysiology is still unclear (12). Also, nervous conduction along both the motor and sensory pathways is not impaired, thus reducing the importance of standard EP studies in disclosing the pathogenetic mechanisms of this disease. However, through the use of specific techniques, EPs have proved useful in testing CNS excitability and sensitization of neurons in the CNS, which have been found to be abnormal in migraine (1). For instance, as...
already mentioned, patients with migraine show a reduced habituation to repetitive sensory stimuli, which explains the higher amplitude of EPs in migraineurs compared to control subjects (13). This phenomenon was initially thought to be caused by an increased cortical excitability. The threshold for phosphen induction by transcranial magnetic stimulation (TMS) of the occipital cortex, lower in patients with migraine than in healthy subjects, seemed to support this hypothesis (14). However, Bohotin et al. (15) recently demonstrated the recovery of a normal habituation pattern of the P100 visual evoked potential (VEP) in migraineurs after high-frequency (10 Hz) repetitive TMS (rTMS) of the occipital cortex. On the contrary, control subjects submitted to low-frequency (1 Hz) rTMS of the occipital cortex showed no P100 amplitude habituation. Given that rTMS at 10 Hz and at 1 Hz increases and reduces cortical excitability, respectively, the authors argued that migraineurs exhibit normal habituation when their cortical excitability is raised to the level of healthy subjects, who, on the contrary, lose VEP habituation if their occipital cortex is inhibited. According to these results, there is cortical hypoxecitability in the migraine interictal phase, and the lack of habituation in migraine patients is explained by the “ceiling effect model” (16), in which habituation depends on the pre-activation level of the cerebral cortex, which being very low in migraine, does not allow any further reduction of excitability. The level of cortical pre-activation is regulated by state-setting brainstem systems, including the serotonergic projections whose role in migraine pathogenesis has been widely demonstrated (17). It is remarkable that cerebral cortex habituation tends to normalize in proximity of the migraine attack (18). Seen in this light, the attack may be a resetting of the system, serving to counter the accumulation of toxic substances in the cerebral cortex, and thus to protect the brain. Although neurophysiological studies have helped to clarify the physiopathology of migraine, the possible application of their results in the clinical field is, as yet, very limited. Kropp and Gerber (18,19) showed that habituation of the contingent negative variation (CNV), a long-lasting wave representing the preparation, at CNS level, for the execution of a task following an imperative stimulus, was lower in migraine patients than in control subjects. Since CNV habituation tends to normalize immediately before the migraine attack (18), the same authors proposed that this parameter might be used to predict attacks (20). However, whereas in most neurophysiological studies the differences between patients with headache and healthy subjects, or between patients with different headache types, are sufficient to allow group-based distinctions, they are not strong enough to define cut-off points beyond which a subject may be diagnosed as suffering from a given primary headache. On the other hand, the differential diagnosis of headache is now based on strict clinical criteria (21), which are generally adequate to distinguish between the different headache types. Therefore the development of neurophysiological instruments would not constitute major progress in this field. In spite of the large number of EP studies in migraine, the function of the brain areas specifically devoted to nociception has been explored only very recently. In general, functional investigation of the human nociceptive system has been hampered by the impossibility of obtaining CNS responses specifically related to the activities of the brain areas involved in nociception. The electrical stimulation of peripheral nerves or of the skin, commonly used to record somatosensory EPs, can hardly be applied to the study of the nociceptive system. Indeed, even if the electrical stimuli were set at painful intensities, both nociceptive and non-nociceptive fibres would be activated, thus making it difficult to differentiate the brain activities specifically related to pain sensation. This problem has been overcome by the introduction of CO₂ LEPs in clinical and neurophysiological practice. Indeed, CO₂ laser pulses are able to activate, specifically, the thin myelinated Aδ and the unmyelinated C fibres, without any concurrent stimulation of the non-nociceptive Aβ afferents (22).

Although the initial reports on LEPs were published more than 20 years ago, this technique has only recently become more widespread and is now used in several laboratories. The main component (Fig. 1) evoked by laser pulses to the skin is a biphasic (negative-positive) complex, whose main amplitude on the Cz vertex occurs at a latency of around 200 ms (N2) and 350 ms (P2) after hand stimulation (23,24). It is preceded by a negative potential (N1) in the temporal region contralateral to the stimulated side and, almost simultaneously, by a frontal positive wave (P1) (latency of around 150 ms after hand stimulation). The N2 and P2 potentials, which are strongly affected by manipulation of the subject’s attention level, are probably related to the emotional component of pain. Studies on LEP generators showed that the N2 and P2 responses are mostly generated by neurons in the cingulate cortex (25), which is part of the limbic system and is important in the emotional component of sensation (26,27). On the contrary, the middle-latency N1 and P1 waves, which are the counterparts of a single dipolar source in the second somatosensory area (25), are less influenced by distraction and might represent the neurophysiological correlate of the sensory component of pain.

![Figure 1 - LEPs after right hand stimulation in a healthy subject. Cz, contralateral temporal (T3) and Fz traces are shown. Arrows indicate the middle-latency N1 and P1 components and the late N2/P2 biphasic vertex complex.](image-url)
CO₂ LEPs in migraine

It is only in recent years that LEPs have been applied in migraine research and their results are summarized here.

**Laser evoked potentials in migraine**

In migraine, LEPs have been studied during the migraine attack and in the interictal phase. In both cases, no impairment of the nociceptive pathways was found (28,29). Indeed, the N1, P1, N2, and P2 components, as well as the scalp topography, were similar in patients and control subjects. The LEP components recorded after skin stimulation at noxious intensities have proved to be generated by inputs transmitted by Aδ fibres. Abnormalities of LEP latency or amplitudes were demonstrated in diseases involving the peripheral Aδ afferents or the central spinothalamic pathway, and showed a strict correlation with loss of pain sensation (30). Hence, since migraineurs do not show hypoalgnesia either in the pain-free period or during attacks, we may expect LEPs not to be dampened. During the attack, compared to the interictal phase, the pain threshold to laser pulses was reduced and the amplitude of the vertex complex (N2/P2) was increased after stimulation of both the hand and the face ipsilateral and contralateral to the pain (28). This finding has been replicated by the same authors in subsequent papers, although it was limited to the symptomatic side (31,32). Moreover, it was shown that the amplitude increase involves, in particular, the positive component (P2) of the biphasic vertex complex (31,32). Interestingly, an N2/P2 amplitude increase, associated with a pain threshold decrement, was found in migraineurs during headache induced by oral administration of nitroglycerin (33). The meaning of this finding is not immediately clear. Since migraine patients show cutaneous hyperalgesia and allodynia within the referred pain area, probably due to central sensitization of spinal tract neurons with periorbital receptive fields, compounded by additional sensitization of third-order thalamic neurons (34), an LEP amplitude increase would be expected. However, experimental data in man have demonstrated a reduction of the vertex LEP amplitude in the presence of cutaneous hyperalgesia and allodynia induced by application of a capsaicin cream to the skin (35). Moreover, also in patients with neuropathic pain of different aetiologies, the presence of hyperalgesia and allodynia is associated with a lower N2/P2 amplitude, compared to healthy subjects (36). On the contrary, an LEP amplitude increase was found in patients suffering from non-organic pain, such as fibromyalgia (37), and from psychogenic pain (36). Therefore, the N2/P2 amplitude increase in migraine is not related to hyperalgesia and allodynia, but probably expresses a hypervigilance to painful stimuli in migraineurs. This hypothesis is also supported by the reversal of the P2 amplitude reduction during the migraine attack after the oral administration of a dose of almotriptan or lysine acetyl-salicylate, in spite of the persisting hyperalgesia (31).

Whether the LEP amplitude increase during the attack is a specific migraine trait, or instead a pain phenomenon, remains unresolved. To answer this question, the nitroglycerin model would seem to be a suitable approach. Indeed, since oral administration of nitroglycerin can induce a migraine-like attack also in healthy subjects, it would be interesting to record LEPs during this headache. Were the LEP amplitude increase observed in migraineurs specific to the migraine disease, no LEP change or amplitude decrement would be observed in healthy subjects.

In a very recent study, de Tommaso et al. (32) compared LEP topography and dipolar sources in the migraine attack and in the interictal phase. In particular, they focused on the vertex positive component (P2) whose topography was explained by a dipole in the anterior cingulate cortex (ACC), thus confirming previous results (25). During the migraine attack, in LEPs obtained after stimulation of the supraorbital zone ipsilateral to the pain, this dipole was shifted towards the rostro-caudal portion of the ACC. In healthy subjects, LEPs to stimulation of an area of hyperalgesia, induced by topical application of a capsaicin cream, change their topography with the P2 distribution becoming more posterior, compared to the baseline (before hyperalgesia). Dipolar analysis shows that the ACC source moves backwards after hyperalgesia induction (35). These experimental results suggest that, in migraineurs, the presence of facial hyperalgesia during the migraine attack does not correlate with the rostro-caudal movement of the ACC source, which may be related to the activation of an ACC portion mainly devoted to processing the emotional component of painful stimuli (32). However, these interesting findings need to be confirmed, since we cannot rule out the possibility that the P2 topographic change occurring during the attack is due to modification of sources outside the ACC. Previous studies on LEP dipolar modeling indicate that the ACC source is not sufficient to explain the P2 topography, which also derives from the activity of a bilateral dipole probably in the insular cortex (25). These further sources should be considered in order to interpret correctly the P2 topographic change that occurs during the migraine attack.

During the interictal phase, LEPs showed a lower habituation in migraine patients than in healthy subjects and patients with tension-type headache (TTH) (29). Habitation was studied by measuring the changes in LEP amplitudes across three consecutive repetitions of 30 trials each (the repetitions lasted 5 min and were separated by 5-min intervals) stimulating the hand and face on both the right and left sides. While a reduction in amplitude of the vertex N2/P2 complex after repetitive noxious stimulations had been previously demonstrated in healthy subjects (38), the behaviour of the N1 amplitude after repetitive stimuli had never been investigated. Valeriani et al. (29) demonstrated that in control subjects the N1 amplitude was progressively reduced after hand stimulation, although this decrement was not as marked as that of the vertex N2/P2 components. A significant N1 habituation was not observed after face stimulation, probably due to the lower number of stimuli used for trigeminal LEP (13) compared to hand LEP (30) recording. In patients with migraine, the habituation of the N2/P2 components was significant after stimulation of the hand, but not of the face. Moreover, when the N2 and P2 amplitudes recorded in the second and third repetitions were compared with those of control subjects, significantly high-
er values were found in migraine patients after both face and hand stimulation (Fig. 2). These results suggest that the cortical areas involved in pain processing show abnormal excitability in migraineurs during the interictal phase, and that this dysfunction, although predominant in the face representation, also involves the cortical projections of other parts of the body, such as the hand. Furthermore, the middle-latency N1 component showed less habituation in the migraine patient group than in the healthy subjects. This finding, rather than reflecting affective-motivational changes, probably represents a specific marker of an abnormal excitability of the sensory cortex in migraine. In TTH patients, the LEP habituation was very similar to that of control subjects, and in migraine patients it was significantly less than in TTH patients. Therefore, the reduced habituation in migraineurs cannot be interpreted as an unspecific epiphenomenon of pain, but is probably linked to the pathophysiological mechanisms underlying the migraine disease and may constitute the background to the development of the migraine attack. Interestingly, Valeriani et al. (29) calculated an LEP habituation index in healthy subjects and set the upper normal limit at the mean value +2 standard deviations. An abnormal habituation index was observed in more than 50% of migraine patients and in no TTH patients.

Figure 2 - LEP amplitude habituation in control subject (upper traces) and in a migraine patient during the interictal phase (lower traces). While a N2/P2 habituation is evident in the healthy subject, the migraineur shows just a small N2/P2 amplitude decrease across the repetitions [modified from Valeriani et al. (29)].
CO₂ LEPs in migraine

(Fig. 3). This result confirms that LEP habituation in migraineurs is greatly different from that seen in TTH patients and healthy subjects, but also shows that reduced LEP habituation cannot be used for the differential diagnosis of headaches in clinical practice, since around 50% of migraine patients show habituation within normal limits. De Tommaso et al. (39) investigated the stimulus intensity dependence of the LEP amplitude and the effect of a distractive task on LEP amplitude in patients with chronic migraine (CM), in patients with episodic migraine without aura (EM), and in healthy subjects. In the CM patients, compared not only with the normal subjects, but also with the EM patients, there was a reduced increment of the N2/P2 component when the stimulus intensity was increased above the detection threshold of the laser pulse to produce a pinprick sensation. Since in normal subjects the peak-to-peak amplitude of the N2/P2 component correlates significantly with the perceived intensity, the vertex LEPs may indeed represent the integrated CNS processing that underlies the perception of pain. Therefore, the authors suggested that a complex disturbance in the cortical processing of pain sensation may underlie the particular pattern observed in CM patients. Interestingly, a similar behaviour of the LEP amplitude may also occur in EM patients when they are stimulated in the supra-orbital region, since the percentage increment of the N2/P2 wave due to the change of stimulus intensity from detection to pain threshold shows an intermediate value, between those of the CM group and the controls. It is thus probable that this phenomenon evolves as the disease itself develops.

Another result in both EM and CM patients was a reduced inhibitory effect of distraction from the painful stimulus on the N2/P2 amplitude (Fig. 4). This effect was evident in normal subjects and was attributed to a reduction of perceived intensity during a cognitive task. The incapacity to reduce the elaboration of the pain sensation during alternative cognitive tasks appears to be a generalized phenomenon in migraine patients, present at both supra-orbital and hand level. It is probably due, in migraineurs, to a hypervigilance to painful stimuli, which, therefore, occurs not only during the attack (see above), but also in the interictal phase.

![Figure 3 - Scatterplot of the habituation index in control subjects (CS), migraine patients (MP), and patients with tension-type headache (THP). Each subject is represented by two symbols, referring to the index obtained for hand and face stimulation. The horizontal line indicates the normal limit (mean + 2 SD), which is exceeded in 13 MP after stimulation of at least one site. In contrast, all THP remain within the normal limits [from Valeriani et al. (29)].](image)

![Figure 4 - Vertex LEPs recorded from a normal subject, a patient suffering from migraine without aura, and a patient with chronic migraine. The left side shows the LEPs from the right hand; the right side shows the scalp potentials obtained from the right supra-orbital zone. LEPs are recorded in the three conditions of subjective pain sensation (black line), perceptive threshold (light grey line), and arithmetic task (dark grey line). The cognitive task produces a higher LEP amplitude decrease in the healthy subject than in the patient with chronic migraine. The patient with episodic migraine shows an intermediate behaviour [from de Tommaso et al. (39)].](image)

Concluding remarks and future perspectives

Thus far, only a few studies have investigated LEPs in migraine. An LEP amplitude increase was found during the migraine attack (31,32). This finding does not seem to be related to the presence of hyperalgesia, but it may indicate a hypervigilance of migraine patients to painful stimuli. Such hypervigilance to pain in migraineurs is supported by the lower effect of a distractive task on LEP amplitude, compared to healthy subjects (39). This characteristic is possibly linked to the paroxysmal nature of the pain, rather than to the pathophysiological mechanisms of the disease. As mentioned above, the change in LEP topography during the migraine attack (32) still needs to be investigated in depth, and appears to be an interesting issue. Whether it may reflect a migraine-specific mechanism or just a pain epiphenomenon may be ascertained through studies on LEP topography during migraine-like pain in healthy subjects (i.e., after oral administration of nitroglycerin). The reduced LEP habituation in migraine patients confirms previous results obtained using different methods (13). It is worth noting...
that reduced LEP habituation was also observed in patients suffering from so-called cardiac syndrome X (CSX) (40). Particularly during effort, CSX patients experience thoracic pain, associated with electrocardiographic ischaemic signs, in spite of the absence of any demonstrable coronary dysfunction. The reduced habituation to experimental pain suggests an abnormal excitability of the nociceptive cerebral cortex in CSX patients, as well as in migraineurs. This abnormality, observed in two different pathological situations, which have only the presence of paroxysmal pain in common, might represent a “predisposition” to pain. In other words, it could represent a common background, on which local trigger factors may act to provoke different diseases characterized by non-neuropathic pain.

In conclusion, the neurophysiological investigation of the human central nociceptive system, made possible by LEP recording, is surely promising in migraine. Study of LEP topography and LEP dipolar sources can disclose plastic changes within the CNS, which might help to explain the transformation of migraine into chronic daily headache, and thus to further understanding of chronic pain mechanisms. Moreover, while LEP studies have, to date, enrolled only patients suffering from migraine without aura, future investigations will have to search for possible differences in pain processing between migraineurs with and without aura. LEP modifications during the migraine attack have been shown to be reversed by drug administration (31), therefore LEPs may be useful in testing the effectiveness and mechanism of action of new pharmacological treatments for the attack. In spite of these possible advantages of future LEP studies in migraine, the present results do not suggest that LEP recording will prove useful in migraine diagnosis. Indeed, although the observed LEP modifications clearly distinguish migraine patients as a group from healthy subjects and from patients with non-migraine headache, there is always a considerable overlap between the groups, which makes it impossible to categorize a single individual as a migraineur, or not.

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