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Laser evoked potentials in patients with trigeminal disease: The absence of Aδ potentials does not unmask C-fibre potentials

A. Truini[a,b], G. Cruccu[a,*]

[a] *Department of Neurological Sciences, "La Sapienza" University, Viale Universita, 30, 00185 Rome, Italy*
[b] *Department of Neurological Sciences, IRCCS San Raffaele, Rome, Italy*

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Abstract

Objective: Although laser stimuli activate both Aδ- and C-fibres, the corresponding laser evoked potentials (LEPs) remain restricted to the Aδ-fibre input. Previous studies found C-LEPs after limb stimulation only in subjects with block or clinical impairment of Aδ-fibres. In this study, we aimed at verifying whether in the trigeminal territory the impairment of Aδ-fibres unmasks the C-LEP.
Methods: By collecting retrospectively LEPs recorded in 370 patients, we analyzed the results from 150 trigeminal divisions with absent Aδ-LEPs.
Results: We found signals that were consistent with the C-fibre input in three patients only. In most patients with absent Aδ-LEPs, however, laser stimuli still elicited the Aδ-conveyed pinprick sensation.
Conclusions: The preserved pinprick sensation suggests that the Aδ-fibre volley, though weakened, reached the cortex. The C-LEP absence may be explained according to the *first come first served* hypothesis: the evoked potential related to an afferent volley reaching the cortex shortly after a preceding input (i.e. a C-fibre volley coming after an Aδ-fibre) will be suppressed.
Significance: In clinical studies using the standard laser pulses to evoke the Aδ-LEPs, the finding of absent signals does not indicate a concomitant impairment of C-fibres.

Keywords: Laser evoked potentials; First come first served; Aδ-fibres; C-fibres; Trigeminal neuropathy

1. Introduction

Infrared laser pulses concomitantly activate Aδ and C nociceptors (Bromm and Lorenz, 1998; Kakigi et al., 2005) and produce a dual perception: a first pinprick sensation related to Aδ-fibre activation, followed by a burning and poorly localized sensation related to C-fibre activation (Bromm and Lorenz, 1998). However, scalp recordings only show evoked responses in the Aδ-fibre latency range, with no signal consistent with C-fibre activation. Experimental studies demonstrated that C-LEPs are "unmasked" by abolishing the Aδ-fibre input with a pressure nerve block (Bromm et al., 1983), by stimulating the tiny skin surfaces where the probability of finding Aδ receptors is very low (Plaghki and Mouraux, 2003), or by heating the skin at temperatures below the Aδ-receptor threshold (Magerl et al., 1999; Cruccu et al., 2003). In some patients, the impairment of myelinated fibres unmasked the C-LEPs (Treede et al., 1988; Lankers et al., 1991; Valeriani et al., 2004).

In any case, C-LEPs only appear if the Aδ fibres are not activated. Spinal inhibition, selective attention and refractoriness of cortical generators have been called upon to account for C-LEP masking (Arendt-Nielsen, 1990; Kakigi et al., 2005; Mouraux and Plaghki, 2007).

Over the last years we got the impression that in the trigeminal territory the clinical impairment of Aδ fibres does not unmask the C-LEP. Our previous studies suggest that the C-LEP can only be obtained by low intensity laser stimuli which heat the skin at temperatures below the Aδ-receptor threshold (Cruccu et al., 2003). In a recent study, we

* Corresponding author. Tel.: +39 06 49694209;fax: +39 06 49914758.
E-mail address: cruccu@uniroma1.it (G. Cruccu).

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reported a patient with trigeminal neuropathy characterized by a severe damage to the myelinated fibres and sparing of C-fibres: whereas laser pulses set to selectively excite C receptors did elicit normal C-LEPs, standard laser pulses for Aδ-LEP recording failed to evoke any signals (Truini et al., 2007a).

To verify our anecdotal impression that in the trigeminal territory the absence of Aδ-LEPs did not unmask the C-LEP, we did a retrospective, systematic search of previous recordings in patients with absent Aδ-LEPs, looking for the presence of signals compatible with C-related activity.

2. Methods

We retrospectively analyzed trigeminal-LEPs recorded in 370 patients (women 246, men 124, 20–88 years) with sensory disturbances and/or pain involving the face during the period from February 2005 to October 2007. Seventy-four patients had a classical trigeminal neuralgia, 16 patients had a symptomatic trigeminal neuralgia, 120 patients had idiopathic trigeminal sensory disturbances and pains; in this condition burning mouth syndrome, temporomandibular disorders, atypical facial pain, trigeminal autonomic cephalalgias and idiopathic trigeminal hypoesthesia and paresthesia are included. Twelve patients had trigeminal sensory hypoesthesia and/or paresthesia related to multiple sclerosis, 24 peripheral neuropathy, 47 trigeminal postherpetic neuralgia, 6 Wallenberg syndrome, 9 isolated symmetrical trigeminal neuropathy, 62 traumatic or iatrogenic damage to the trigeminal peripheral nerves. In all patients, LEPs were studied by using a neodymium:yttrium–aluminium–perovskite laser (Nd:YAP) (wavelength 1.34 mm, pulse duration 2–20 ms, maximum energy 7 J) with fibre-optic guidance. We used laser pulses of relatively high intensity (119–178 mJ/mm^2), short duration (5 ms), and small diameter (~5 mm), eliciting in normal subjects pinprick sensations related to Aδ-fibre activation. According to the specific clinical problem laser pulses were directed to the supraorbital and/or the perioral regions. The laser beam was slightly shifted after each stimulus. The interstimulus interval varied pseudorandomly (10–15 s). Subjects lay on a couch and wore protective goggles. To determine the laser perceptive threshold, we delivered a series of stimuli at increasing and decreasing intensity, and defined the perceptive threshold as the lowest intensity at which the subjects perceived at least 50% of the stimuli. The main Aδ-LEP complex, N2-P2, was recorded from the vertex (Cz) referenced to the nose. From 10 to 20 trials devoid of artefacts were collected and averaged off line. We measured peak latency and amplitude (peak-to-peak) of the main N2-P2 vertex complex. The first step was to select trigeminal divisions with absent Aδ-LEPs: this was accomplished by the staff nurse relying on the computer-stored medical reports that were given to the patients. The second step was to identify a C-fibres related signal in the stored recordings: this was accomplished by two independent neurophysiologists (i.e. other than the authors) according to the presence of reproducible signals, with a minimum amplitude of 5 μV, in a time window from 200 to 650 ms.

3. Results

Seventy-eight patients had absent Aδ-LEPs: 14 had classical trigeminal neuralgia, 9 symptomatic trigeminal neuralgia, 2 idiopathic trigeminal pain, 4 trigeminal sensory hypoesthesia related to multiple sclerosis, 2 peripheral neuropathy, 27 postherpetic neuralgia, 4 Wallenberg syndrome, 9 isolated idiopathic trigeminal neuropathy, and 7 had traumatic or iatrogenic damage to trigeminal branches. These data corresponded to 72 perioral (V2 and V3 trigeminal divisions) and 78 supraorbital regions (V1 trigeminal division) with absent Aδ-LEPs (Table 1). Fig. 1 shows findings in a representative subject. Laser stimuli were perceived as pinprick sensations, except for 2 patients who had a clear burning sensation and two who reported a sensation that was difficult to describe. We could detect a brain signal compatible with C-fibres related activity only in 3 patients (isolated idiopathic trigeminal neuropathy, trigeminal neuralgia, and facial pain without evident causes), which corresponds to five divisions out of the 150 with absent Aδ-LEPs (3%). C-LEPs were recorded in 2 patients who perceived a burning sensation and in one who reported a sensation that was difficult to describe.

4. Discussion

Our study indicates that in the trigeminal territory the absence of Aδ-LEPs does not unmask C-LEPs. Naturally some trigeminal nerve diseases such as Wallenberg syndrome, herpes zoster, or peripheral neuropathy may affect both Aδ- and C-fibres to a similar extent, thus dampening both Aδ- and C-LEPs. However, other conditions are characterized by the sparing of C-fibres. Multiple sclerosis lesions are restricted to the myelinated fibres (Love et al., 2001), traumatic or iatrogenic lesions of the trigeminal branches mainly involve larger fibres, which are more sensitive to compression. In classical trigeminal neuralgia, C-fibres are supposed to be unaffected by the compression exerted by the neurovascular conflict. In patients with isolated symmetrical trigeminal neuropathy, supraorbital nerve biopsy showed a severe reduction of myelinated fibres and the selective sparing of unmyelinated fibres (Cruccu et al., 2003; Truini et al., 2007a). Although all these patients had spared C-fibres and absent Aδ-LEPs, the laser stimuli failed to evoke reproducible C-LEPs.

This finding contrasts with the previous studies that found C-LEPs after limb stimulation in subjects with block or clinical impairment of Aδ-fibres (Bromm et al., 1983; Treede et al., 1988; Lankers et al., 1991).

Table 1
Frequency of absent Aδ-LEPs and unmasked C-LEPs

	V1	V2/V3	Total
Number of examined trigeminal divisions	532	622	1154
Absent Aδ-LEPs	78 (15%)	72 (12%)	150 (13%)
Unmasked C-LEPs	2 (2.6%)	3 (4.2%)	5 (3.3%)

However, whereas in those studies laser stimuli elicited only a warm or burning sensation, in our subjects with absent Aδ-LEP laser stimuli almost always evoked a pinprick sensation, often followed by a burning sensation. These data indicate that in our subjects the Aδ- fibre input was severely impaired but not completely abolished. Probably the spared fibres were too few to yield a scalp potential, but enough to generate a pinprick sensation. Were the C-LEP occlusion exerted by the full engagement of the same cortical generators, such a great reduction of the Aδ-fibre input (able to abolish the Aδ-LEP), would be probably sufficient to unmask the C-LEP. Hence, we hypothesized that the lack of C-LEPs in patients with absent Aδ-LEP could be explained by the *first come first served* phenomenon (Garcia-Larrea, 2004; Truini et al., 2007b). According to this theory LEPs, as well as other EPs (Näätänen and Picton, 1987), represent the output of networks detecting rapid energy changes relative to a preceding baseline. The output of such networks depends both on the time elapsed between successive inputs and the input intensity. In our case, the response to an afferent volley reaching the cortex shortly after a preceding input (i.e. a C-fibre volley coming after the Aδ-fibre) will be suppressed (Garcia-Larrea, 2004; Truini et al., 2007b).

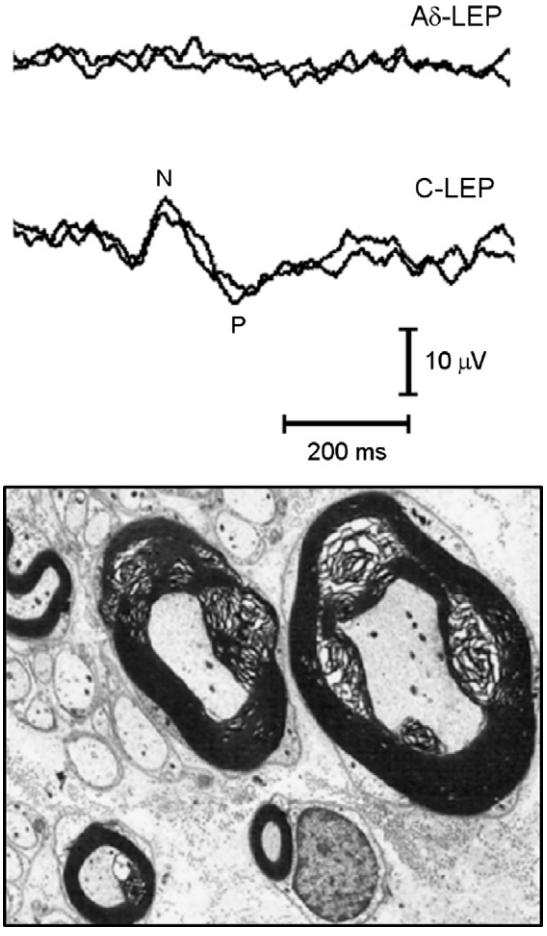

Fig. 1. Laser evoked potential and histological findings in a patient with isolated symmetrical trigeminal neuropathy selectively affecting the myelinated fibres. Upper panel: LEP study after perioral stimulation in a patient with trigeminal neuropathy. Standard laser pulses set to elicit Aδ-LEPs failed to evoke any cerebral signal. Normal C-LEPs were recorded by using a technique of selective stimulation of C receptors (Cruccu et al., 2003). Lower panel: electron microscopy of a supraorbital nerve fascicle showing simil-Wallerian degeneration of myelinated fibres and normal unmyelinated fibres. Note one spared, normal Aδ fibre (close to a Schwann-cell nucleus).

A recent study reported the simultaneous recording of both Aδ- and C-LEPs after trigeminal territory stimulation in patients with peripheral neuropathy related to Fabry disease (Valeriani et al., 2004). Although this finding seems to be in contrast with ours, patients with Fabry disease have a relative overflow of C-fibre input (Valeriani et al., 2004), thus the unmasking of C-LEPs in these patients may be explained by an increased C-fibre afferent volley.

We recorded brain signals compatible with C-fibre-related activity only in three patients. We cannot exclude that these signals, being of a longer latency than the Aδ-LEP, were related to impaired Aδ-fibres with a reduced conduction velocity. However, these patients did not perceive Aδ-fibres related pin-prick sensation, rather two of them perceived a burning sensation, which is related to C fibres. Furthermore in the patient with isolated symmetrical trigeminal neuropathy a supraorbital nerve biopsy showed a very severe reduction of Aδ-fibres. In any case, the general message of this study would only be strengthened if even the rare C-LEPs that we found were nothing else than delayed Aδ-LEPs.

Our retrospective study demonstrates that in the trigeminal territory an Aδ-fibre impairment does not unmask C-LEPs, and thus it does not give any information on the function of C-fibres. This finding may be explained by the *first come first served* phenomenon (Garcia-Larrea, 2004). Probably only a complete damage to the Aδ-fibre pathway, with abolishment of the pinprick sensation, may unmask the C-LEP.

With hand or foot stimulations the longer latency difference between the two volleys will attenuate the *first come first served* phenomenon. Still, this mechanism can – to an uncertain extent – hold true for body territories other than the face. In clinical studies using the standard laser pulses to evoke the Aδ-LEPs, the finding of absent signals does not warrant a concomitant impairment of C-fibres. This can be demonstrated only by using the techniques of selective stimulation. If these are unavailable, the subjective perception is more reliable.

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