Experimental Neurology 223 (2010) 609–614

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Descending volleys generated by efficacious epidural motor cortex stimulation in patients with chronic neuropathic pain

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ARTICLE INFO

Article history:
Received 26 January 2010
Accepted 17 February 2010
Available online 24 February 2010

Keywords:
Cortical stimulation
Corticospinal tract
Motor cortex
Neuropathic pain
Spinal cord
Stimulation parameters
Transcranial magnetic stimulation

ABSTRACT

Epidural motor cortex stimulation (EMCS) is a therapeutic option for chronic, drug-resistant neuropathic pain, but its mechanisms of action remain poorly understood. In two patients with refractory hand pain successfully treated by EMCS, the presence of implanted epidural cervical electrodes for spinal cord stimulation permitted to study the descending volleys generated by EMCS in order to better appraise the neural circuits involved in EMCS effects. Direct and indirect volleys (D- and I-waves) were produced depending on electrode polarity and montage and stimulus intensity. At low-intensity, anodal monopolar EMCS generated D-waves, suggesting direct activation of corticospinal fibers, whereas cathodal EMCS generated I2-waves, suggesting transsynaptic activation of corticospinal tract. The bipolar electrode configuration used in chronic EMCS to produce maximal pain relief generated mostly I3-waves. This result suggests that EMCS induces analgesia by activating top–down controls originating from intracortical horizontal fibers or interneurons but not by stimulating directly the pyramidal tract. The descending volleys elicited by bipolar EMCS are close to those elicited by transcranial magnetic stimulation using a coil with posteroanterior orientation. Different pathways are activated by EMCS according to stimulus intensity and electrode montage and polarity. Special attention should be paid to these parameters when programming EMCS for pain treatment.

Introduction

Epidural motor cortex stimulation (EMCS) with surgically implanted electrodes was proposed in the early nineties as a treatment of chronic, drug-resistant neuropathic pain (Tsubokawa et al., 1991). A meta-analysis recently confirmed the therapeutic potential of EMCS (Lima and Fregni, 2008), but its mechanisms of action remain poorly understood. At the site of stimulation, EMCS likely activates fibers of passage that are more excitable than local neuronal cell bodies (Ranck, 1975; Nowak and Bullier, 1998; McIntyre and Grill, 2002). However, there is uncertainty about the type of recruited fibers. Recruitment depends on fiber diameter, orientation (parallel or normal to the cortical surface), distance to the stimulating electrode, and electrode polarity. Modeling studies predict that cathodal EMCS would excite horizontal fibers that run in the superficial layers of the motor cortex (Manola et al., 2005, 2007). Another approach to this question is to study the descending volleys that are elicited by cortical stimulation. These volleys can be recorded at the level of the spinal cord and consist of direct (D-) and indirect (I-) waves (Patton and Amassian, 1954). D-waves reflect direct activation of pyramidal axons, whereas I-waves reflect transsynaptic activation of the corticospinal tract. In fact, these descending volleys have complex origins (see Amassian and Stewart, 2003; Di Lazzaro et al., 2004a for review) and represent a mixture of early excitatory post-synaptic potentials and axon discharges, followed by prolonged inhibitory post-synaptic potentials (Rosenthal et al., 1967; Amassian et al., 1987).

In the context of pain treatment, the descending volleys elicited by EMCS have been previously investigated in only two studies (Di Lazzaro et al., 2004b; Yamamoto et al., 2007). However, these two studies presented some limitations (see Discussion) and no firm conclusions could be drawn about the type of descending volleys really involved in the analgesic effects of EMCS. In the present study, we have revisited this issue by recording the descending volleys evoked by monopolar and bipolar EMCS in two patients who experienced excellent pain relief following EMCS therapy. Special attention was paid to the influence of stimulus intensity and electrode montage according to the parameters used for chronic therapeutic stimulation. The descending volleys generated by EMCS were compared to those generated by transcranial magnetic stimulation

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doi:10.1016/j.expneurol.2010.02.008

(TMS), providing control data in agreement with the literature (Kaneko et al., 1996; Nakamura et al., 1996; Di Lazzaro et al., 2004a).

Methods

The two patients enrolled in this study have been treated by spinal cord stimulation (SCS) prior to EMCS. In these patients, a quadripolar SCS lead (Pisces Quad model 3487A, Medtronic, Minneapolis, MN, USA) had been implanted percutaneously in the cervical dorsal epidural space to treat unilateral, distal, upper limb pain. The first patient, a 32-year-old woman, had refractory pain of the left thumb, secondary to traumatic metacarpophalangeal luxation with open reduction and various postoperative local complications. A diagnosis of complex regional pain syndrome (CRPS) type II was proposed. She presented hyperpathia and both thermal and mechanical allodynia in the painful area. Pain syndrome was severe and drug-resistant. Four years after onset, she underwent treatment by chronic cervical SCS. The second patient, a 54-year-old man, had refractory pain of the right hand, secondary to traumatic lesion of brachial plexus (car injury). He presented a mild sensory deficit with mechanical allodynia but no motor deficit in the painful zone. Pain syndrome was unsuccessfully treated by various drugs for 14 years before chronic cervical SCS was tried.

Unfortunately, cervical SCS did not provide clinical benefit in these patients. Three to four years after SCS implantation, EMCS therapy was offered to these patients, since this technique can produce satisfactory neuropathic pain relief, even in case of SCS failure (Cruccu et al., 2007). Two quadripolar epidural leads (Resume II, model 3587A, Medtronic) were implanted perpendicular to the central sulcus, over the motor cortical region corresponding to the painful hand (Fig. 1). Intraoperative image-guided navigation and electrophysiological mapping were performed as previously described (Nguyen et al., 1999).

Because SCS was not efficacious, both patients asked to remove the system: SCS extension wires and pulse generator were removed under general anesthesia within 1 month after EMCS implantation, while EMCS lead was still externalized. The patients gave their informed consent for the realization of electrophysiological testing during this intervention.

To increase the reliability of intraoperative recordings, the infusion of anesthetic agents (propofol and remifentanil) was carefully monitored to maintain the bispectral index (BIS) around a value of 60. Electrical cortical stimulation was performed by using contacts of the Resume EMCS leads that were numbered 0 to 3 for the medial lead and 4 to 7 for the lateral lead. Contacts 0 and 4 were the most anterior, and contacts 3 and 7, the most posterior. The stimulation consisted of single square waves of 0.1-ms duration and was delivered by connecting lead contacts to the constant current stimulator of a Keypoint EMG machine (Alpine Biomed, Skovlunde, Denmark). In patient 1, all bipolar and monopolar (anodal and cathodal) configurations were tested but only for the lateral lead that was best placed over hand motor region. In patient 2, only monopolar configurations were tested but for the two leads. For monopolar stimulation, the reference electrode was a subcutaneous needle electrode placed in the occipital region, to avoid direct activation of face muscles by the stimulation. The ground electrode was placed around the forearm with a Velcro strap.

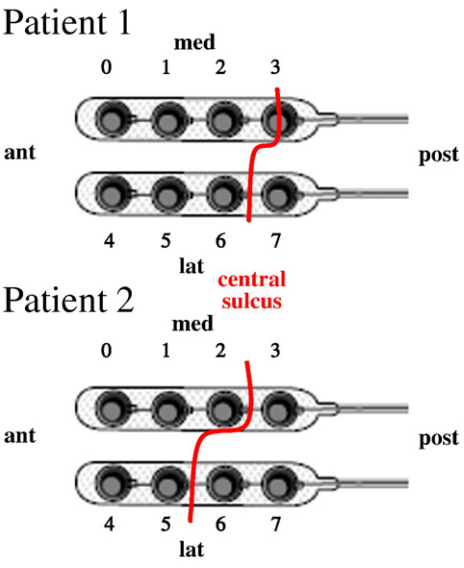

Fig. 1. Position of the quadripolar leads in epidural stimulation of the motor cortex in both patients. A red line indicates the position of the central sulcus, as determined by image-guided navigation and phase reversal of somatosensory-evoked potentials.

Monophasic TMS of the motor cortex was performed with a Magstim 200 stimulator and a figure-of-eight coil with external loop diameters of 90 mm (Magstim Co., Carmarthenshire, UK). The coil was held over the motor cortex at the optimum scalp position to elicit motor-evoked potentials (MEPs) at the painful hand (surface recordings over the first dorsal interosseus muscle). Two different orientations of the coil were tested, with the induced current flowing in either lateromedial (LM) or posteroanterior (PA) direction.

Whatever the type of stimulation (epidural electric or transcranial magnetic), descending volleys were averaged from 10 single stimuli delivered at an intensity that was maintained just below the threshold for producing motor responses at the painful hand. In patient 1, one trial of epidural stimulation was performed at high (suprathreshold) intensity with the montage selected for chronic therapeutic stimulation. In all cases, descending volleys were recorded bipolarly using the most proximal and distal contacts of the cervical SCS lead (30-mm center-to-center distance). The signal was amplified and filtered (bandpass, 20 Hz–2 kHz) using a Keypoint EMG machine (the same as for electrical cortical stimulation trial). The latency of each component of the descending volleys was measured to its peak as usual. Only consistent deflections with mean amplitude of 2 μV were analyzed.

Finally, the level of pain was assessed before and 1 year after EMCS implantation using a visual analogue scale (VAS) and the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994; Keller et al., 2004). The patients were given a pain diary and were asked to self-rate everyday the mean pain intensity that they experienced over daytime on a 0–100 VAS (from 0, no pain, to 100, the highest imaginable pain). For analyses, the seven daily pain ratings preceding each visit were averaged. The BPI provides information on the degree to which pain interferes with seven different functions (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Interference was rated for each item on a 0–100 scale (from 0, pain does not interfere, to 100, pain completely interferes), and the mean score was taken for analysis.

Results

Clinical results

In patient 1, the mean preoperative VAS score was 100/100 on weekly evaluation and BPI was 43/100. Analgesic drugs were morphine sulfate (100 mg/day) and topiramate (25 mg/day). One month after implantation, the mean VAS score was 40/100, and BPI was 37/100. Parameters of stimulation were 40 Hz (frequency), 60 μs (pulse duration), and 2 V (amplitude). The montage was 2–3 + 6–7+ (numbers indicating the contacts, and + and – the anodes and cathodes, respectively). One year after implantation, the mean VAS score was 20/100 and BPI was 6/100, while stimulation parameters and montage remained unchanged. Pain scores improved by 80–86% compared to preoperative baseline. Analgesic drugs were changed to

a reduced dose of morphine sulfate (30 mg/day) and tramadol (200 mg/day).

In patient 2, the mean preoperative VAS score was 100/100 on weekly evaluation and BPI was 93/100. Analgesic drugs were morphine sulfate (60 mg/day) and hydroxyzine (25 mg/day). One month after implantation, the mean VAS score was 20/100 and BPI was 38/100. The parameters of stimulation (40 Hz, 60 μs, 2 V) and the montage (2–3 + 6–7+) were the same as in patient 1. One year after implantation, the mean VAS score was less than 10/100 and BPI was 18/100, while stimulation parameters and montage remained unchanged. Pain scores improved by 81–100% compared to preoperative baseline without modification in analgesic medication.

Spinal cord recordings

Monophasic TMS delivered to the motor cortex (at about 45% of stimulator output, just below motor threshold) produced D-waves (latency: 2.3–2.4 ms) with an LM-oriented figure-of-eight coil and I-waves (latencies ranging from 4.3 to 9.2 ms) with a PA-oriented coil (Fig. 2). These results are consistent with those previously published in the literature (Kaneko et al., 1996; Nakamura et al., 1996; Di Lazzaro et al., 2004a).

Regarding EMCS, anodal monopolar stimulation (at about 10 mA, just below motor threshold) produced an early wave of which latency (2.9–3.2 ms) was 0.6–0.8 ms longer than that of the D-wave produced by TMS (2.3–2.4 ms) (Fig. 2). Cathodal monopolar stimulation evoked a later wave, which had almost the same latency as the I2-wave produced by TMS (6.0–6.8 ms) (Fig. 2). In patient 1, bipolar stimulation evoked a combination of I-waves that were mostly I3-waves (in eight out of 10 tested configurations) and less often I1- or I2-waves (in two and three configurations, respectively) (Fig. 3). In this patient, the electrode montage used for chronic EMCS (6–7+) evoked only I2- and I3-waves at low intensity (Fig. 3) and all three I-waves as well as D-waves at high (suprathreshold) stimulus intensity (Fig. 4).

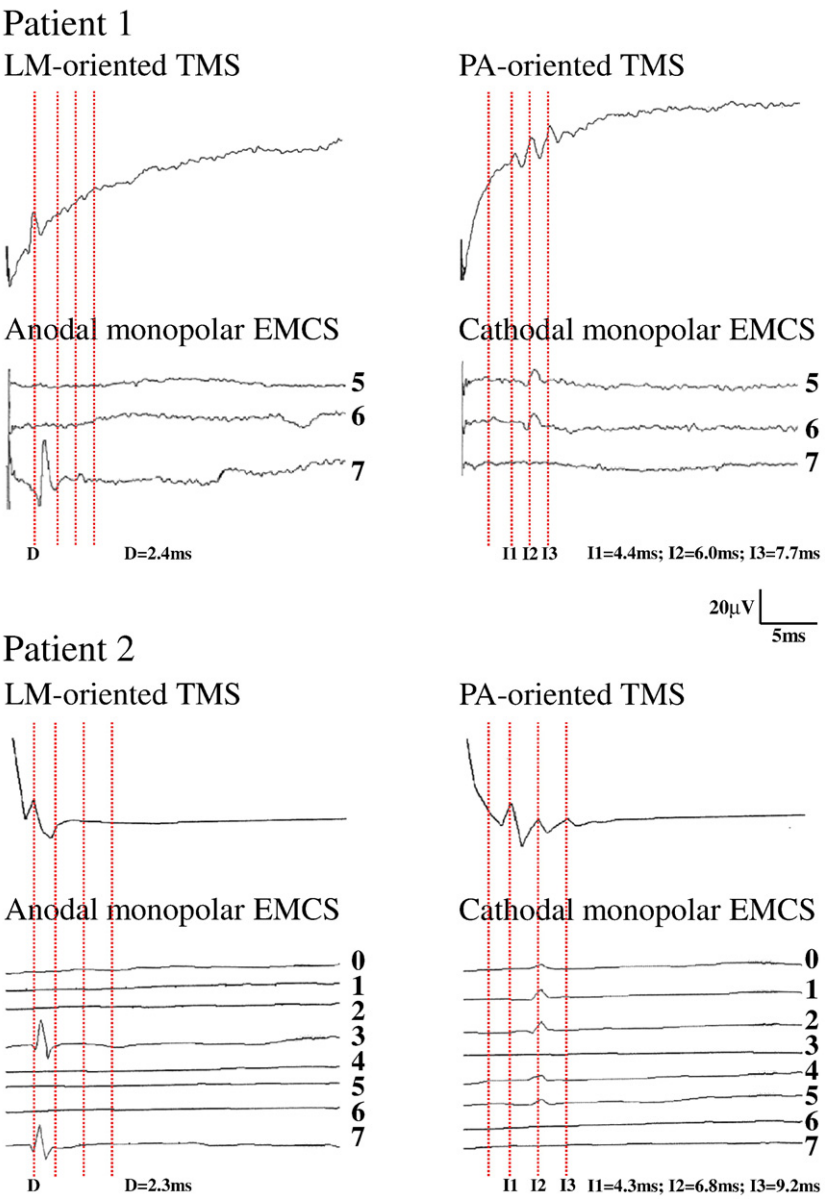

Fig. 2. Descending volleys recorded from cervical spine in both patients and generated by (i) transcranial magnetic stimulation (TMS) with lateromedial (LM) or posteroanterior (PA) coil orientation and (ii) anodal and cathodal monopolar epidural motor cortex stimulation (EMCS). Vertical dotted lines indicate peak latencies of direct (D-waves) and indirect (I-waves) volleys. In patient 1, only the most lateral quadripolar lead has been tested (contacts 4–7). Contact 4 did not evoke any response, either as an anode or as a cathode.

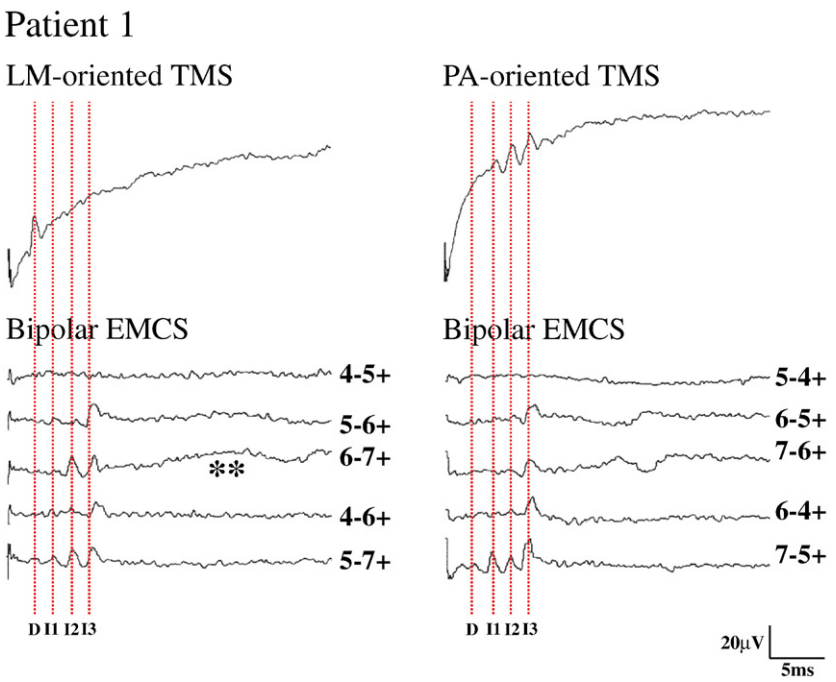

Fig. 3. Descending volleys recorded from cervical spine in patient 1 and generated by (i) transcranial magnetic stimulation (TMS) with lateromedial (LM) or posteroanterior (PA) coil orientation and (ii) bipolar epidural motor cortex stimulation (EMCS). Vertical dotted lines indicate peak latencies of direct (D-waves) and indirect (I-waves) volleys. **Optimal montage used for chronic stimulation (cathode: contact 6; anode: contact 7).

Discussion

Low-intensity cathodal EMCS produced I2-waves, reflecting transsynaptic activation of corticospinal tract fibers. Conversely, low-intensity anodal EMCS produced D-waves, reflecting direct activation of corticospinal tract fibers. These D-waves were delayed by 0.6–0.8 ms compared to those produced by LM-oriented TMS. A similar delay (0.4 ms) was observed by Di Lazzaro et al. (2004b) using high-intensity bipolar EMCS. Compared to TMS, EMCS could recruit slower conducting fibers or excite corticospinal fibers at a more proximal site.

Low-intensity bipolar EMCS mostly produced I3-waves and not a combination of D- and I2-waves. These results suggest that bipolar stimulation is not simply a "bifocal" stimulation that would have corresponded to the addition of the responses to monopolar anodal and cathodal stimulations. Anodal and cathodal electrical fields likely overlap and the neuronal activity produced near the anode and near the cathode, respectively, can interact with each other (Holsheimer et al., 2007b). The magnitude of these interactions depends on the center-to-center distance between the electrodes.

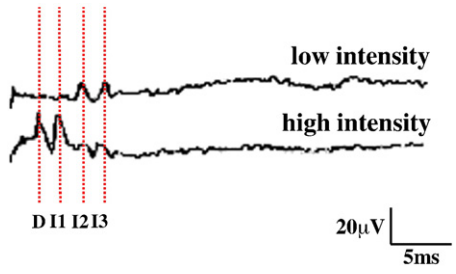

Fig. 4. Descending volleys recorded from cervical spine in patient 1 and generated by the optimal configuration for chronic epidural motor cortex stimulation (6–7+) with stimulation intensity set below or above motor threshold. Vertical dotted lines indicate peak latencies of direct (D-waves) and indirect (I-waves) volleys.

All these results were obtained while stimulation intensity was maintained below motor threshold as in EMCS therapy for chronic pain. The existence of descending corticospinal volleys without concomitant MEPs may be surprising. In fact, MEP monitoring in spinal cord surgery showed that the abolition of MEPs is not necessarily associated with a decrease in D-wave amplitude (Kothbauer et al., 1998). These observations reveal that descending corticospinal volleys are not sufficient to produce MEPs in a fully relaxed muscle of a patient under general anesthesia.

The bipolar EMCS configuration providing optimal chronic pain relief produced mostly late I-waves at low intensity (below motor threshold) and also D- and early I-waves at high intensity (above motor threshold). As stimulus intensity increased, the induced electrical field likely spreads and goes deeper into the brain, recruiting more fibers. For example, motor cortex TMS performed at high intensity can produce D-waves initiated at the axonal hillock of pyramidal cells in addition to I-waves, even using a PA-oriented figure-of-eight coil (Di Lazzaro et al., 1998). In our experience, EMCS efficacy does not improve by increasing stimulation intensity, possibly because analgesic effects relate to the activation of fibers in the superficial cortical layers. Increasing the intensity of stimulation would in that case result in the recruitment of additional circuits that are not necessarily involved in the control of pain. It was hypothesized that EMCS could produce analgesia by recruiting horizontal fibers in the upper cortical layers of precentral gyrus rather than by directly exciting the pyramidal tract (Manola et al., 2005, 2007). The present results confirm this hypothesis, since we found that EMCS produced late I-waves at the intensity and with the montage used for chronic stimulation.

Two studies have previously investigated the descending volleys produced by EMCS. The study of Di Lazzaro et al. (2004b) differed from ours, since the patient was conscious (not anesthetized), the epidural electrode was parallel to the central sulcus (not perpendicular), and the pain was of central origin (not peripheral) and located at the face (not at the hand). Nevertheless, these authors found like us that suprathreshold (high-intensity) EMCS generated D-waves and several I-waves with the bipolar montage selected for chronic

therapeutic stimulation. However, they did not study the descending volleys generated by bipolar EMCS at lower stimulus intensities, as used for chronic therapeutic stimulation.

Later, Yamamoto et al. (2007) found in two patients with post-stroke pain treated by EMCS that the site of stimulation producing the best pain relief corresponded to the location of the cortical contacts evoking the largest D-waves. However, these D-waves were obtained in response to monopolar anodal stimulation with a 20-contact grid during a screening period, whereas chronic therapeutic stimulation was performed with a quadripolar Resume electrode and bipolar montage. In addition, D-waves were produced by using 0.2-ms duration monophasic rectangular stimuli delivered at very low frequency (2 Hz) and high (suprathreshold) intensity (30 mA). These parameters of cortical stimulation were fully unusual for chronic therapeutic EMCS. Therefore, Yamamoto et al. (2007) did not demonstrate that therapeutic EMCS elicited D-waves, but only that recording D-waves to suprathreshold anodal stimulation could help to determine the optimal site for chronic stimulation. We found a similar result using a different approach in a previous study (Holsheimer et al., 2007a). The best contact for chronic EMCS was the contact evoking the largest MEPs in the painful territory when selected as an anode during intraoperative testing with monopolar stimulation performed at high (suprathreshold) intensity (Holsheimer et al., 2007a). In addition, we demonstrated that this contact should be selected as a cathode for chronic therapeutic stimulation. This was consistent with the hypothesis that analgesic effects are associated with transsynaptic rather than direct activation of the corticospinal tract fibers.

The descending volleys produced by the optimal EMCS configuration for pain treatment are closer to those produced by PA-oriented TMS than LM-oriented TMS. It is known that LM-oriented TMS preferentially recruits D-waves at low intensity, whereas PA-oriented TMS recruits I-waves (Kaneko et al., 1996; Nakamura et al., 1996; Di Lazzaro et al., 2004a). This finding was fully confirmed in the present study.

It has been shown that repetitive TMS (rTMS) applied to the motor cortex could produce analgesic effects in patients with chronic neuropathic pain (see Lefaucheur, 2006 for review). In this application, rTMS is usually performed by handling the figure-of-eight coil with PA orientation. Moreover, it was recently demonstrated that PA-oriented rTMS, but not LM-oriented rTMS, was more effective than placebo (André-Obadia et al., 2008). The present study provides a physiological basis for these results and confirms that EMCS and PA-oriented TMS likely activate similar neural circuits. It is therefore tempting to consider that motor cortex rTMS and EMCS could share the same mechanisms of action to relieve pain. This reinforces the value of PA-oriented rTMS as a tool to provide predictive factor for the outcome of subsequent EMCS therapy (Lefaucheur et al., 2004; André-Obadia et al., 2006; Hosomi et al., 2008). AP-oriented TMS should be even more effective, since it evokes later I-waves than PA-oriented TMS, at least in some patients (Di Lazzaro et al., 2001).

The present study also confirms that descending volleys of action potentials produced by EMCS below motor threshold intensity can reach the spinal cord. Stimulation of the motor cortex was previously shown to modulate nociceptive spinal activities, such as the nociceptive flexion reflex (RIII) in pain patients (García-Larrea et al., 1999) or the activity of wide dynamic range (WDR) neurons in the dorsal horn of rats (Senapati et al., 2005). This is consistent with a top–down inhibition of dorsal horn neurons involved in pain processing, maybe via the activation of brainstem structures, such as the periaqueductal grey matter (García-Larrea and Peyron, 2007).

Before coming to a conclusion, several limitations should be acknowledged. Firstly, the patients were treated with several drugs, and recordings were performed under general anesthesia. Possible effects of analgesic or anesthetic drugs cannot be excluded. Secondly, we did not study the descending volleys generated by EMCS in patients in whom EMCS therapy was not as successful as in the present patients. Therefore, we cannot certify that the results we obtained were specifically associated with therapeutic efficacy of EMCS and did not only reveal unspecific EMCS effect. In other words, neural pathways mediating the analgesic effects of EMCS are not necessarily the same as those involved in the late I-waves that were evoked. Thirdly, special attention was paid to stimulus intensity and electrode montage with respect to chronic EMCS settings, but descending volleys were recorded in response to single pulses, whereas EMCS for pain relief is performed at 40 Hz. Repetitive stimulation may modify the pattern of descending volleys, but these volleys can be recorded and reliably analyzed only in response to single shocks. One possibility was to record the descending volleys to single shocks before and after a period of 40-Hz EMCS. However, the analgesic effects produced by EMCS occur with a delay of several hours or days beyond the period of stimulation (Nguyen et al., 1999). To perform cervical spinal recordings before and after such a prolonged period of cortical stimulation was not possible. We thought that looking for changes in the amplitude or nature of the descending volleys after a brief period of 40-Hz EMCS could not give relevant information on how EMCS works, and finally, we have not performed such an experiment.

Conclusion

We have analyzed the descending volleys evoked by EMCS with parameters of stimulation close to those used for therapy, at least regarding stimulus intensity and electrode montage. EMCS did not activate directly the corticospinal tract but generated late I-waves, suggesting activation of intracortical interneurons. The present study confirms the influence of stimulus intensity and electrode montage and polarity on the nature of the neural pathways activated by EMCS. This must be taken into account in analyzing the results of EMCS for the treatment of chronic pain. In practice, careful attention should be paid to the location of the epidural contacts selected as anode(s) and cathode(s) and to the intensity of stimulation used for chronic EMCS.

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