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Effects of spinal cord stimulation on cortical excitability in patients with chronic neuropathic pain: A pilot study

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Abstract

Background: Despite a broad clinical use, the mechanism of action of SCS is poorly understood. Current information suggests that the effects of SCS are mediated by a complex set of interactions at several levels of the nervous system including spinal and supraspinal mechanisms.
Aims: The study was undertaken to investigate the influence of SCS on distinct parameters of cortical excitability using single- and paired-pulse transcranial magnetic stimulation (TMS).
Methods: Five patients with chronic neuropathic pain were examined with the SCS stimulator on and off by means of TMS. Pain was assessed using a visual-analogue scale. Electrophysiological and pain parameters of patients during this procedure were compared by means of a linear mixed effect model.
Results: SCS induced a significant modulation of cortical excitability, especially by influencing the parameter "intracortical facilitation" ($t = -2.657$; df = 8; $p = 0.029$). A significant relationship between this parameter and "perceived pain" could be obtained ($t = -4.798$; df = 8; $p = 0.002$).
Conclusions: These results suggest that SCS is able to influence neurobiological processes at the supraspinal level and that clinical effects of SCS may be at least in part of cortical origin.

Keywords: Spinal cord stimulation; Transcranial magnetic stimulation; Cortical excitability; Neuropathic pain

1. Introduction

Spinal cord stimulation (SCS) has been demonstrated to have useful therapeutic pain-relieving effects in a number of painful syndromes (Monhemius and Simpson, 2003; Cameron, 2004; Taylor, 2006; Stanton-Hicks, 2006; Van Buyten, 2006; Ubbink and Vermeulen, 2006; Buchser et al., 2006). The best results can be achieved in patients with chronic, non-malignant pain syndromes of neuropathic origin (Simpson, 1991). Due to a relatively simple implantation combined with the possibility to control stimulation parameters by the patient, SCS has emerged to a widely used treatment method, especially when pharmacotherapy and anaesthesiological blocks failed to relieve pain syndromes (Cameron, 2004; Turner et al., 2004). However, the understanding of the mode of action of SCS is still fragmentary (Meyerson and Linderoth, 2000). The gate control theory postulated a spinal modulation of noxious inflow (Melzack and Wall, 1965). Furthermore, the integrity of the dorsal column-lemniscal

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system seems to be a prerequisite for the effectiveness of SCS (Sindou et al., 2003). Additionally, in line with current theoretical conceptualizations of pain processing (Melzack, 1999) SCS has been shown to affect pain processing at the supraspinal level encompassing cortical structures such as the thalamus or the anterior pretectal nucleus (Gildenberg and Murthy, 1980; Roberts and Rees, 1994; Oakley and Prager, 2002; Linderoth et al., 2005). Active participation of these cortical structures in pain processing may contribute to SCS related pain relief. One mode of action as evidenced in animal structures may base on SCS induced activation of the anterior pretectal nucleus, which has descending pain inhibitory influences on lower segments (Roberts and Rees, 1994). For this reason, pain relieving SCS effects are considered to reflect the contribution of multiple neurobiological mechanisms at distinct levels of the central nervous system (Oakley and Prager, 2002). Neurochemically, SCS seems to strengthen inhibitory gamma-aminobutyric acid (GABA) mediated mechanisms finally leading to an attenuation of pain induced central hyperexcitability (Meyerson and Linderoth, 2000; Petersen-Felix and Curatolo, 2002; Lind et al., 2004).

Transcranial magnetic stimulation (TMS) represents a non-invasive neurophysiological tool to assess different aspects of cortical excitability and to give insight into the nature and localization of inhibitory and excitatory processes within cortical networks (Hallett, 2000). TMS has been successfully applied to study cortical effects of distinct clinical approaches using electric stimulation such as vagus nerve stimulation (Di Lazzaro et al., 2004) or deep brain stimulation (Cunic et al., 2002).

Using TMS we evaluated the effects of SCS on cerebral cortex excitability in patients with chronic neuropathic pain.

2. Methods

2.1. Patients

We investigated five patients with permanently implanted SCS devices (Medtronic-GmbH, Düsseldorf, Germany) due to neuropathic pain syndromes. All patients had suffered from radiating pain in one or both legs corresponding to the L5 and/or the S1 dermatome at least 2 years prior to SCS implantation. One patient (VP) presented with additional chronic low back pain equalling the intensity of the pain in both S1 dematomes Treatment strategies including pharmacotherapy, radiofrequency of facet joints or psychotherapy had failed to alleviate pain decisively (Table 1). In all five patients an objective basis for the pain complaint was present and there was no active disease necessitating other specific surgical or medical treatment. Trial stimulations have been performed for 5–7 days and pain relief >50% was achieved in all cases. Major psychological and psychiatric disorders were excluded prior to the test stimulation. Due to pronounced variations of stimulation intensities depending on body positions the 4-electrodes wire lead has been replaced by an 8-electrodes lead paddle in one patient (VP) and by an 4-electrodes lead paddle in another (HA). The first five SCS patients of our outpatient clinic who gave their written informed consent to the study were included. The study was conducted according to the declaration of Helsinki and was approved by the university's ethical committee.

2.2. Procedure

Experimental procedures were based on those described previously (Eichhammer et al., 2004; see Fig. 1). TMS was performed with two high-power Magstim 200 magnetic stimulators connected to a Bistim Module (Magstim Co., Whitland, Dyfed, UK). A figure-of-eight coil was held over the left motor cortex to elicit motor responses in the contralateral right abductor digiti minimi (AMD) muscle. Thus, a cortical area including the C8 myotom was stimulated by TMS. During the study, muscle relaxation was monitored with continuous auditory feedback of the amplified EMG signal. We evaluated (1) resting motor threshold (RMT), an overall measure of corticospinal excitability (Hallett, 2000); (2) cortical silent period (CSP), which reflects primarily inhibitory GABA-B-mediated processes (Siebner et al., 1998) within the sensorimotor loop, probably at the level of the basal ganglia and the thalamus (Moll et al., 2001; Munchau et al., 2002);

Table 1
Patient characteristics and histories

Patient initials	Age years	Gender	Medication for pain	Diagnosis	Duration of pain	SCS implantation
VP	45	F	Buprenorphine, amitryptiline gabapentin	Lumbosacral root injury syndrome	4 years	10/2003
HL	50	M	None	Lumbosacral root injury syndrome	2 years	6/2003
HA	48	M	Morphine, gabapentin and doxepine	Lumbosacral root injury syndrome	10 years	7/2001
BD	39	M	Morphine	Lumbosacral root injury syndrome	16 years	10/1997
TW	41	M	Tramadole clomipramine olanzapine	Lumbosacral root injury syndrome	7 years	12/2003

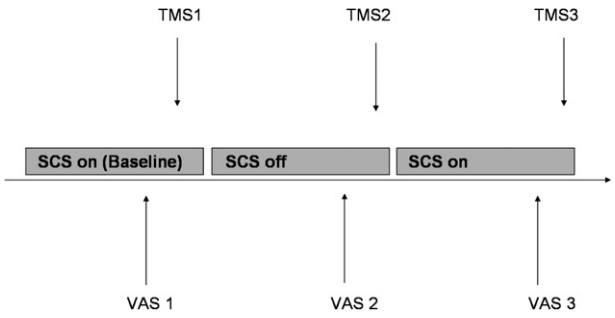

Fig. 1. Time course of TMS and VAS measurements (TMS = transcranial magnetic stimulation; VAS = measurement of pain intensity according to a visual analogue scale).

and (3) intracortical inhibition (ICI) und intracortical facilitation (ICF), reflecting the excitability of inhibitory GABA-A-ergic and excitatory glutamergic cortical circuits (Hallett, 2000).

RMT was determined according to Rossini and colleagues (Rossini et al., 1994) and defined as the lowest intensity at which at least 5 of 10 successive pulses produced a motor evoked potential (MEP) of 50 μV or more. To ensure comparable results with other TMS studies, MT was measured by approaching from suprathreshold intensities and reducing in steps of 1% stimulator output.

Cortical silent period (CSP) was obtained at stimulus intensities 50% above RMT according to published studies (Berardelli et al., 1996). Duration of the CSP was defined as the time from end of the MEP to the return of any voluntary electromyographic activity.

Intracortical inhibition (ICI) and intracortical facilitation (ICF) were obtained according to previously published protocols (Ziemann and Hallett, 2000), using interstimulus intervals of 2 and 3 ms (ICI) and 7 and 15 ms (ICF).

A 10 cm visual-analogue scale (VAS) as has been described previously (Scott and Huskisson, 1976) was used to evaluate the patients' pain.

All TMS parameters as well as pain values were determined under three conditions: First, as a baseline measurement during permanent active stimulation, then 20 min after inactivation of the device ("off"-condition) and again 20 min after reactivation of SCS ("on"-condition). All patients were studied under a stable medication, which was unchanged at least four weeks prior to the beginning of the study.

2.3. Statistical analysis

The analysis of TMS parameters and pain values in patients under baseline condition and with the stimulator off and on was performed using a linear mixed effect model. For repeated measures this statistical approach has been shown to be superior compared to classical repeated measures analysis of variance techniques in various situations (Brown and Prescott, 1999).

3. Results

All five patients with chronic neuropathic pain completed the procedure. SCS led to a significant modulation of cortical excitability during the three conditions (baseline – "off-phase" – "on"-phase) as indexed by the TMS parameter "ICF" ($t = -2.657$; $df = 8$; $p = 0.029$). As compared to baseline, ICF increased during the "off"-condition and was reverted after reactivation of the stimulator (see Fig. 2). Evaluation of perceived pain as measured by VAS showed the same sequential pattern with the highest pain scores during the "off" condition. Statistically, a significant relationship between "perceived pain" and measures of ICF could be obtained ($t = -4.798$; $df = 8$; $p = 0.002$).

Enhancement of ICI and prolongation of CSP during the "on" phase of SCS as compared to the "off" condition, reflected an SCS induced augmentation of inhibitory processes, however without reaching statistical significance (ICI: $t = -1.319$; $df = 8$; $p = 0.224$; CSP: $t = -1.491$; $df = 8$; $p = 0.174$; see Table 2a,b). In contrast to these parameters, RMT was not modified by SCS at all ($t = -0.175$; $df = 8$; $p = 0.866$).

4. Discussion

To the best of our knowledge, this is the first study using TMS to investigate effects of SCS on cortical excitability in patients with chronic neuropathic pain. The principal finding is that SCS is able to efficiently modulate cortical excitability, especially by influencing ICF. Modulation of this TMS parameter is closely associated with an alteration in pain experience. In particular, reactivation of the SCS device after an "off" period led to a

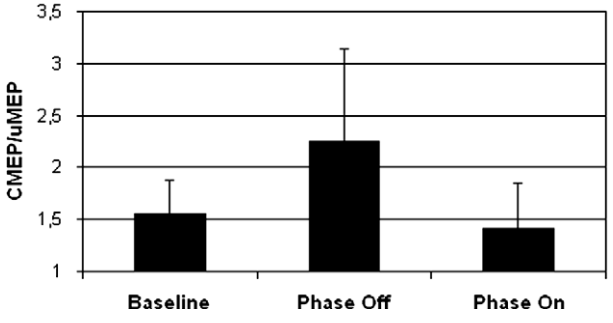

Fig. 2. Intracortical Facilitation (ICF) Effects of SCS on intracortical facilitation (ICF): ICF in patients during baseline conditions (with the stimulator permanently on) and during the two different phases of SCS (phase "off" and phase "on"). ICF is given as conditioned MEP(cMEP)/unconditioned (uMEP) ratio (y-axis).

Table 2a
Results of the three different TMS measurements during baseline spinal cord stimulation (1), stimulation off (2) and again stimulation on (3): resting motor threshold (RMT) intracortical inhibition (ICI), intracortical facilitation (ICF) and cortical silent period (CSP)

Patient	VAS 1 (Baseline; SCS on)	VAS 2 (SCS off)	VAS 3 (SCS on)	RMT1	RMT2	RMT3	ICI1	ICI2	ICI3
VP	7.3	8.5	6.8	42	50	49	1.19557604	2.16618657	1.90094891
HL	2.5	5.3	1.4	60	59	59	0.12950034	0.3860514	0.27420601
HA	6	6.3	4.1	64	64	59	0.51176914	0.46123794	0.49090455
TW	7.1	7.8	7	44	50	53	0.54495436	0.47684383	0.55643944
BD	4.5	6.5	4.4	46	54	51	0.53301756	0.62225494	0.39763629
Mean	5.48	6.88	4.74	51.2	55.4	54.2	0.58296349	0.82251494	0.72402704
Standard deviation	2.00	1.27	2.29	10.06	6.07	4.60	0.38403479	0.75598735	0.66641704

Please note that lower ICI values indicate strengthening of inhibitory processes. VAS values represent pain intensities on the visual analogue scale.

Table 2b

Patient	ICF1	ICF2	ICF3	CSP1	CSP2	CSP3
VP	1.48044848	2.56692851	2.05675602	90	104	131
HL	1.27140787	1.35055602	0.8246564	174	142	148
HA	2.11093044	2.34084952	1.3087545	150	148	131
TW	1.45212203	3.54238355	1.49287051	133	134	162
BD	1.49588603	1.44904101	1.38472849	110	170	144
Mean	1.56215897	2.24995172	1.41355318	131.4	139.6	143.2
Standard deviation	0.31971204	0.89853872	0.44119559	32.9	24.0	13.0

marked decrease in cortical excitability, primarily indicated by a reduction of ICF, and paralleled by a relief in pain experience.

ICF is known to reflect cortical processes mediated by glutamatergic *N*-methyl-D-aspartate (NMDA) related mechanisms (Ziemann and Hallett, 2000). Animal studies underline the pivotal role of these NMDA mediated processes in the occurrence of cortical plasticity (Garraghty and Muja, 1996), which serves an important function in the persistence of pain experience (Flor et al., 1997). Based on these data, our study provides some evidence that SCS might not solely act by influencing pain associated neurobiological processes at the spinal level (Garcia-Larrea et al., 1989; Roberts and Rees, 1994; Meyerson and Linderoth, 2000; Sindou et al., 2003; Linderoth et al., 2005; Meyerson and Linderoth, 2006) but also by modulating excitability and probably NMDA related neuroplasticity at the supraspinal level.

Current data underline the pivotal importance of spinal mechanisms in mediating pain-relieving SCS effects. In this context, Yakhnitsa et al. have demonstrated that SCS may induce a significant and long-lasting inhibition of both the after-discharges and the exaggerated principal response in primarily wide-dynamic range dorsal horn neurons (Yakhnitsa et al., 1999). It was also shown that the threshold of the early component of the flexor reflex, which is Aβ-fiber mediated, is elevated in rats (Meyerson et al., 1995). Cui et al. found a reduced release of excitatory amino acids (glutamate, aspartate) and at the same time an augmentation of the GABA release in the dorsal horn of nerve lesioned rats (Cui et al., 1997). Meyerson and Linderoth provided excellent overviews of the sites and mode of action of spinal cord stimulation in neuropathic pain (Meyerson and Linderoth, 2003; Meyerson and Linderoth, 2006). For this reason, neurobiological effects of SCS at the cortical level as evidenced in our study can be considered to potentially reflect solely reduced excitatory input from the spinal level. This interpretation favours hypothetical concepts in which cortical structures build up a passive system of pain registration. In contrast, more recent theoretical framework emphasizes active participation of supraspinal structures in pain processing (Melzack, 1999). In line with this view, animal studies suggest the importance of supraspinal mechanisms for SCS related clinical effects (El-Khoury et al., 2002). Moreover, supraspinal structures are known to exert descending control over nociceptive dorsal horn neurons (Li and Zhuo, 1998), thereby strengthening concepts which interpret SCS effects as the result of a complex interplay of multiple neurobiological mechanisms at distinct levels of the central nervous system (Oakley and Prager, 2002). The contribution of multiple neurobiological systems to the effectiveness of SCS is additionally illustrated by findings of Sindou et al. (2003) demonstrating that the integrity of the dorsal column-lemniscal system is essential for beneficial effects of SCS and that the central conduction time (CCT) of somatosensory evoked potentials (SSEPs) allows to objectively predict clinical outcome after SCS. In this context, comparing TMS parameters in patients with

and without abnormal CCT may further contribute to disentangle the relevance of spinal and supraspinal mechanisms in the mediation of SCS effects.

At a neurochemical level, SCS may act via upregulation of GABA-mediated inhibitory processes (Cui et al., 1996; Wallin et al., 2002). With regard to our study, reactivation of SCS after an "off" period seems to lead to an augmentation of GABA-A and GABA-B mediated inhibitory mechanisms indicated by an increase in ICI and a prolongation of CSP. Especially increase in CSP during SCS suggests that beside cortical mechanisms, subcortical inhibitory processes, e.g. at the level of the thalamus may be involved in mediating SCS effects (Munchau et al., 2002). In line with this hypothesis, recordings from the human thalamus have demonstrated neurobiological effects during SCS stimulation (Gildenberg and Murthy, 1980). However, SCS induced changes of these TMS parameters did not reach statistical significance in our study. This may be due to methodological issues such as the small sample size, a high interindividual variability of GABA related inhibitory processes in response to SCS stimulation, or to the fact that beside GABA a variety of neurochemical substances are involved in mediating neurobiological effects of SCS (Linderoth et al., 1992). Compatible with our TMS findings, one way to further strengthen SCS induced GABA related inhibitory processes should be the additional administering of central acting GABA agonists. This procedure was successfully applied to patients not responding satisfactorily to SCS, using intrathecal baclofen, a well-known GABA-B receptor agonist (Lind et al., 2004).

In summary, our results suggest that SCS is able to influence neurobiological processes at the supraspinal level and that these cortical processes might contribute to the effectiveness of SCS. This view is in line with animal data and theoretical considerations that multiple neurobiological mechanisms at distinct levels of the CNS contribute to the action of SCS. Further research is needed to elucidate the potential role of supraspinal structures and to identify relevant cortical areas, thereby contributing to a better understanding of SCS action and optimization of treatment.

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