Neuroscience Letters 529 (2012) 80–85

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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

Loss of short-latency afferent inhibition and emergence of afferent facilitation following neuromuscular electrical stimulation

C.S. Mang[a], A.J. Bergquist[b], S.M. Roshko[b], D.F. Collins[b,*]

[a] Brain Behaviour Laboratory, Faculty of Medicine, Department of Physical Therapy, University of British Columbia, Vancouver, British Columbia, Canada
[b] Human Neurophysiology Laboratory, Faculty of Physical Education and Recreation, Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada

HIGHLIGHTS

- Neuromuscular electrical stimulation (NMES) enhances motor cortex (M1) excitability.
- The M1 circuitry involved in this enhanced excitability is not well understood.
- Changes in afferent inhibitory and facilitatory M1 circuits after NMES were tested.
- NMES abolished afferent inhibition and promoted afferent facilitation of M1.
- NMES enhances the excitatory effect of afferent inputs on M1.

ARTICLE INFO

Article history:
Received 11 July 2012
Accepted 16 August 2012

Keywords:
Motor cortex
Corticospinal excitability
Afferent volley
TMS
NMES

ABSTRACT

Neuromuscular electrical stimulation (NMES) increases the excitability of corticospinal (CS) pathways by altering circuits in motor cortex (M1). How NMES affects circuits interposed between the ascending afferent volley and descending CS pathways is not known. Presently, we hypothesized that short-latency afferent inhibition (SAI) would be reduced and afferent facilitation (AF) enhanced when NMES increased CS excitability. NMES was delivered for 40 min over the ulnar nerve. To assess CS excitability, motor evoked potentials (MEPs) were evoked using transcranial magnetic stimulation (TMS) delivered at 120% resting threshold for first dorsal interosseus muscle. These MEPs increased by ~1.7-fold following NMES, demonstrating enhanced CS excitability. SAI and AF were tested by delivering a "conditioning" electrical stimulus to the ulnar nerve 18–25 ms and 28–35 ms before a "test" TMS pulse, respectively. Conditioned MEPs were compared to unconditioned MEPs evoked in the same trials. TMS was adjusted so unconditioned MEPs were not different before and after NMES. At the SAI interval, conditioned MEPs were 25% smaller than unconditioned MEPs before NMES but conditioned and unconditioned MEPs were not different following NMES. At the AF interval, conditioned MEPs were not different from unconditioned MEPs before NMES, but were facilitated by 33% following NMES. Thus, when NMES increases CS excitability there are concurrent changes in the effect of afferent input on M1 excitability, resulting in a net increase in the excitatory effect of the ascending afferent volley on CS circuits. Maximising this excitatory effect on M1 circuits may help strengthen CS pathways and improve functional outcomes of NMES-based rehabilitation programs.

1. Introduction

The afferent volley generated during neuromuscular electrical stimulation (NMES) can increase the excitability of pathways between the motor cortex (M1) and skeletal muscles [2,3,15,18,19]. This enhanced corticospinal (CS) excitability is measured as an increase in amplitude of motor evoked potentials (MEPs) generated by transcranial magnetic stimulation (TMS) and is mediated primarily at the level of the cortex [23]. Such NMES-induced increases in CS excitability start within ~10–20 min of the beginning of an NMES session and can persist for hours after a single session [10,18,19,23] or days after repeated sessions [21]. Persistent increases in CS excitability are thought to represent a

Abbreviations: AF, afferent facilitation; CS, corticospinal; C-T, conditioning-test; EMG, electromyography; FDI, first dorsal interosseus; GABA, gamma-amino-butyric acid; ICF, intracortical facilitation; LAI, long-latency afferent inhibition; M1, motor cortex; MEP, motor evoked potential; NMES, neuromuscular electrical stimulation; PAS, paired associative stimulation; SAI, short-latency afferent inhibition; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

* Corresponding author at: 6-41 General Services Building, University of Alberta, Edmonton, Alberta T6G2H9, Canada. Tel.: +1 780 4926506; fax: +1 780 4922364.
E-mail address: dave.collins@ualberta.ca (D.F. Collins).

0304-3940/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2012.08.072

strengthening of CS pathways and, following NMES are associated with improvements in motor performance [20] and improved functional outcomes of motor training sessions following central nervous system injury [1,11]. The present experiments were designed to explore cortical mechanisms that underlie how the electrically evoked afferent volley generated during NMES increases CS excitability. We assessed the excitability of cortical circuits interposed between the ascending electrically evoked afferent volley and descending CS pathways before and after a session of NMES. We predicted that excitability of inhibitory circuits would decrease, and that of excitatory circuits would increase, when CS excitability was enhanced following NMES.

The cortical circuitry involved in NMES-induced increases in CS excitability has not been thoroughly investigated. A previous study that utilized paired-pulse TMS to investigate the effects of NMES on intracortical inhibitory (short-interval intracortical inhibition, SICI) and excitatory (intracortical facilitation, ICF) circuits found that when NMES increased CS excitability, SICI and ICF were unaltered [12]. Using a method similar to paired-pulse TMS, cortical circuits that mediate transmission between the ascending afferent volley and CS pathways can be tested by delivering a "conditioning" electrical stimulus over a peripheral nerve immediately before a "test" magnetic stimulus over M1. Using this approach, the afferent volley generated by the conditioning stimulus attenuates test MEPs at short conditioning-test (C-T) intervals (~20 ms) and over a range of long C-T intervals (~50–1000 ms), effects termed short-latency afferent inhibition (SAI) [27] and long-latency afferent inhibition (LAI) [3,25], respectively. The MEP can also be facilitated using this paradigm (afferent facilitation, AF) at C-T intervals between those that elicit SAI and LAI [5,6]. The effects of NMES on SAI and AF have not been previously evaluated.

The purpose of the present study was to determine whether SAI and AF are altered when CS excitability is enhanced by NMES. SAI and AF were measured before and after a single session of NMES. NMES was delivered over the ulnar nerve and MEPs recorded from the first dorsal interosseus (FDI) muscle using a protocol that we have previously found to enhance CS excitability [18,19]. We hypothesized that SAI would be reduced and AF enhanced when NMES increased CS excitability. The results of this study contribute to our understanding of how the electrically evoked afferent volley generated during NMES increases CS excitability.

2. Methods

2.1. Participants

Nine healthy right-handed volunteers (4 male, 5 female; age range: 18–48 years) participated in two experimental sessions. The experimental protocol was approved by the Human Research Ethics Board at the University of Alberta. In the first session (~1 h), optimal C-T intervals for SAI and AF were identified. In the second session (~3 h), CS excitability, SAI and AF were tested before and after a 40 min session of NMES. The two experimental sessions were completed within 24 h of one another for a given participant.

2.2. Experimental procedure

All experimental procedures were performed on the right arm. Participants were seated with backs and necks supported and right shoulder, elbow, and wrist joint angles maintained at ~15°, 120° and 180°, respectively. The elbow, wrist and hand were supported in a relaxed position with the angle between the thumb and index finger maintained at ~70°.

2.3. Electromyography (EMG)

EMG was recorded from FDI in the right hand using 1 cm^2 bipolar surface recording electrodes (Vermed Medical, Bellow Falls, Vermont). EMG signals were pre-amplified (500×) and band pass filtered at 10–1000 Hz (NeuroLog system; Digitimer, Welwyn Garden City, Hertfordshire, England). Data were sampled at 5000 Hz with a 12-bit A/D converter (National Instruments, Austin, Texas) and recorded from 100 ms before to 350 ms after electrical stimulus delivery.

2.4. Transcranial magnetic stimulation

MEPs were evoked using TMS (Magpro R30; Medtronic Inc., Minneapolis, Minnesota) applied with a figure-of-eight coil (Medtronic MC-B70, Minneapolis, Minnesota) while participants were relaxed. TMS was delivered with an inter-stimulus interval that varied randomly between 5 and 8 s for all trials. The "hot-spot" for right FDI was found for each participant by moving the coil over left M1 to find the site that elicited the largest amplitude MEP in FDI at the lowest stimulation intensity. This site was recorded using a Brainsight™ image-guided system (Rogue Research, Montreal, Quebec). During all TMS trials the coil was held in place to maintain position and orientation (precision: ±3 mm).

2.5. Afferent-conditioning of MEPs

2.5.1. Conditioning stimuli (ulnar nerve stimulation)

Rectangular pulses of 1 ms duration were delivered to the ulnar nerve at the wrist using a constant current stimulator (DS7A, Digitimer, Hertfordshire, England). The conditioning stimulus intensity was adjusted to just above motor threshold based on the presence of a small (<50 μV) but consistent M-wave in FDI. This intensity was chosen because it was effective in producing SAI and AF in pilot experiments.

2.5.2. Test stimuli (TMS)

MEPs in FDI were evoked as described above. The TMS intensity was adjusted to elicit MEPs that were of relatively consistent amplitude across several consecutive stimuli for a given participant. Between participants, the amplitude of these MEPs ranged from ~1 to 2 mV. This intensity of TMS was used for the test stimulus before the 40 min session of NMES.

2.5.3. Conditioning-test intervals

In pilot experiments, MEPs were inhibited when the peripheral nerve stimulus was delivered at short (~18–25 ms) and long (>40 ms) intervals, consistent with previous descriptions of SAI and LAI [25,27]. Between periods of SAI and LAI a period of AF was identified (~28–35 ms); however, this period of AF was not always characterized by a robust facilitation of the MEP compared to the unconditioned test MEP. Rather, similar to previous research investigating AF [24], many participants demonstrated a loss of inhibition in this time period, where the amplitude of the conditioned test MEP was enhanced compared to the periods of SAI and LAI, but not compared to the unconditioned test MEP (i.e. "disinhibition").

2.6. Determining optimal C-T intervals for each participant (Session 1)

In the first experimental session, 20 unconditioned MEPs and 20 conditioned MEPs at each of 15, 18, 20, 22, 25, 28, 30, 32, and 35 ms C-T intervals were elicited in a randomized order. After visual inspection of these data, two C-T intervals, one that elicited SAI (range: 18–25 ms) and one that elicited AF (range: 28–35 ms),

were identified for each participant for testing in the second experimental session according to the following criteria: (1) there was inhibition and facilitation/disinhibition compared to unconditioned MEPs at the specific C-T interval selected for SAI and AF, respectively, (2) the immediately adjacent C-T intervals showed the same general effect of inhibition or facilitation/disinhibition (i.e. if 22 ms was identified as the SAI C-T interval, then the test MEP was also inhibited at 20 ms and 25 ms C-T intervals), and (3) the C-T intervals for SAI and AF were within ranges described in previous literature [5,6,27] and in pilot experiments.

2.7. Effect of NMES on cortical circuitry (Session 2)

NMES was applied over the right ulnar nerve at the wrist using two stimulation electrodes (3.2 cm round; model CF3200, Axelgaard Manufacturing, Lystrup, Denmark) placed at the site that evoked a response in FDI (M-wave or H-reflex) at the lowest stimulation intensity. Rectangular pulses of 1 ms duration were delivered from a constant current stimulator. NMES was delivered at 100 Hz for 40 min in a 20 s on, 20 s off cycle at an intensity at which a single stimulus evoked an M-wave that was ~15% of the maximally evocable M-wave in FDI [18,19].

Resting MEP threshold was determined before the NMES session, and was defined as the lowest TMS intensity that evoked MEPs in FDI of at least 50 μV in response to 4 of 8 stimuli. To assess whether CS excitability was altered by NMES, 20 MEPs were evoked at this intensity before and after NMES. Specifically, the TMS was delivered at the same intensity (120% of the pre-NMES resting MEP threshold), as percent output, before and after NMES. To assess the effect of NMES on SAI and AF, a block of 60 MEPs, consisting of 20 unconditioned (control) MEPs and 20 conditioned MEPs at each of the C-T intervals for SAI and AF, were elicited before and after NMES. These control and conditioned MEPs (SAI and AF C-T intervals) were delivered in a randomized order. Inhibition evoked by paired-pulse TMS is dependent on test MEP amplitude [16] and thus it is conceivable that this is also the case for SAI and AF. As a result, in the present study a change in test MEP amplitude following the 40 min session of NMES could by itself influence the magnitude of SAI or AF. Thus, to control for changes in SAI and AF elicited by a change in efficacy of the test stimulus after the 40 min session of NMES, TMS intensity was adjusted after NMES to produce a test MEP of similar amplitude to the MEP elicited before NMES. These methods are consistent with previous studies that tested the effects of paired associative stimulation (PAS) on SAI and LAI [22,26]. Stimulus delivery was controlled by a digital timing device developed in LabView (National Instruments, Austin, TX). The order of the block of trials assessing CS excitability and the block of trials assessing SAI and AF were randomized for each participant before and after NMES.

2.8. Data analyses

MEPs were measured peak-to-peak. All statistical analyses were performed on group data. To test for changes in CS excitability, a paired *t*-test was used to compare the amplitudes of the MEPs evoked at 120% resting MEP threshold before and after NMES. To test for changes in SAI and AF, a two-way repeated measures analysis of variance was used to compare the amplitude of the unconditioned MEPs and of the MEPs evoked at the two C-T intervals before and after NMES. The factors for this analysis were Time (2 levels: before and after) and Condition (3 levels: unconditioned, SAI interval, AF interval). For each test, the significance level was set at $p < 0.05$. Fisher's Least Significant Difference post hoc tests were performed when appropriate. All descriptive statistics are reported as mean ± standard error.

3. Results

The amplitude of MEPs evoked at 120% resting threshold increased significantly following NMES. Concurrently, SAI was abolished and AF emerged after NMES.

3.1. CS excitability

Fig. 1A shows MEPs evoked at 120% resting MEP threshold before and after NMES for one participant. For this individual, the mean amplitude of these MEPs was ~3 times larger after NMES than before NMES. The amplitude of MEPs evoked at 120% MEP threshold averaged across all participants before and after NMES are shown in Fig. 1B. For the group, the mean amplitude of MEPs evoked at 120% resting MEP threshold increased ~1.7-fold after the NMES session [$t_{(8)} = -2.72$, $p = 0.03$].

3.2. SAI and AF

Fig. 2A shows MEPs evoked before and after NMES for the same participant whose data are shown in Fig. 1A. Before NMES, MEPs conditioned at the SAI interval were smaller than unconditioned MEPs and MEPs conditioned at the AF interval were of similar amplitude to the unconditioned MEPs on average. After 40 min of

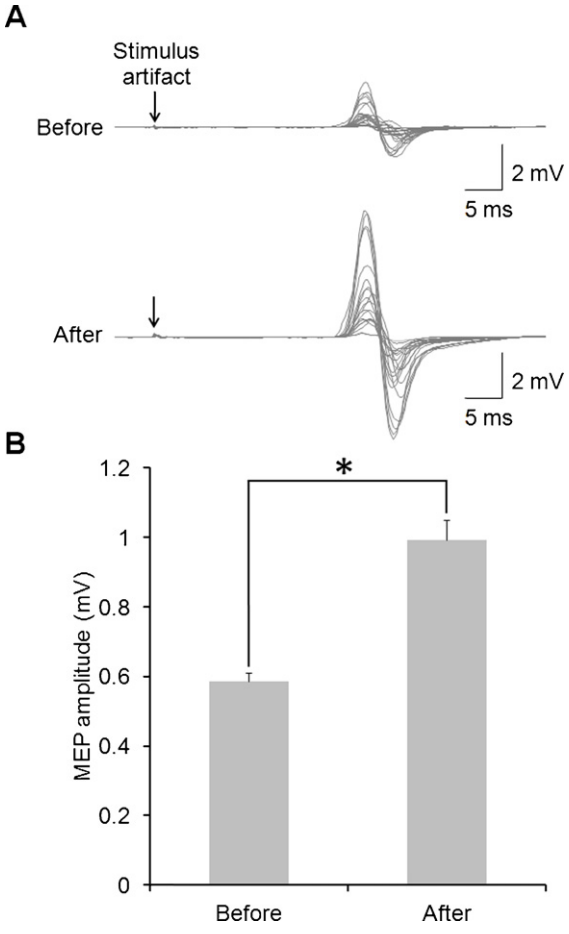

Fig. 1. Amplitude of MEPs at 120% resting threshold before and after a single session of NMES. Panel A shows each MEP waveform (grey lines; $n = 20$) recorded from a single participant before and after NMES when TMS intensity was set at 120% of the resting MEP threshold before NMES. Black arrows indicate the TMS stimulus artifacts. Panel B shows mean MEP amplitude averaged across the group ($n = 9$) before and after NMES when TMS intensity was set at 120% of the resting MEP threshold before NMES. Black bars and asterisks indicate comparisons that are significantly different ($p < 0.05$). Error bars represent one standard error.

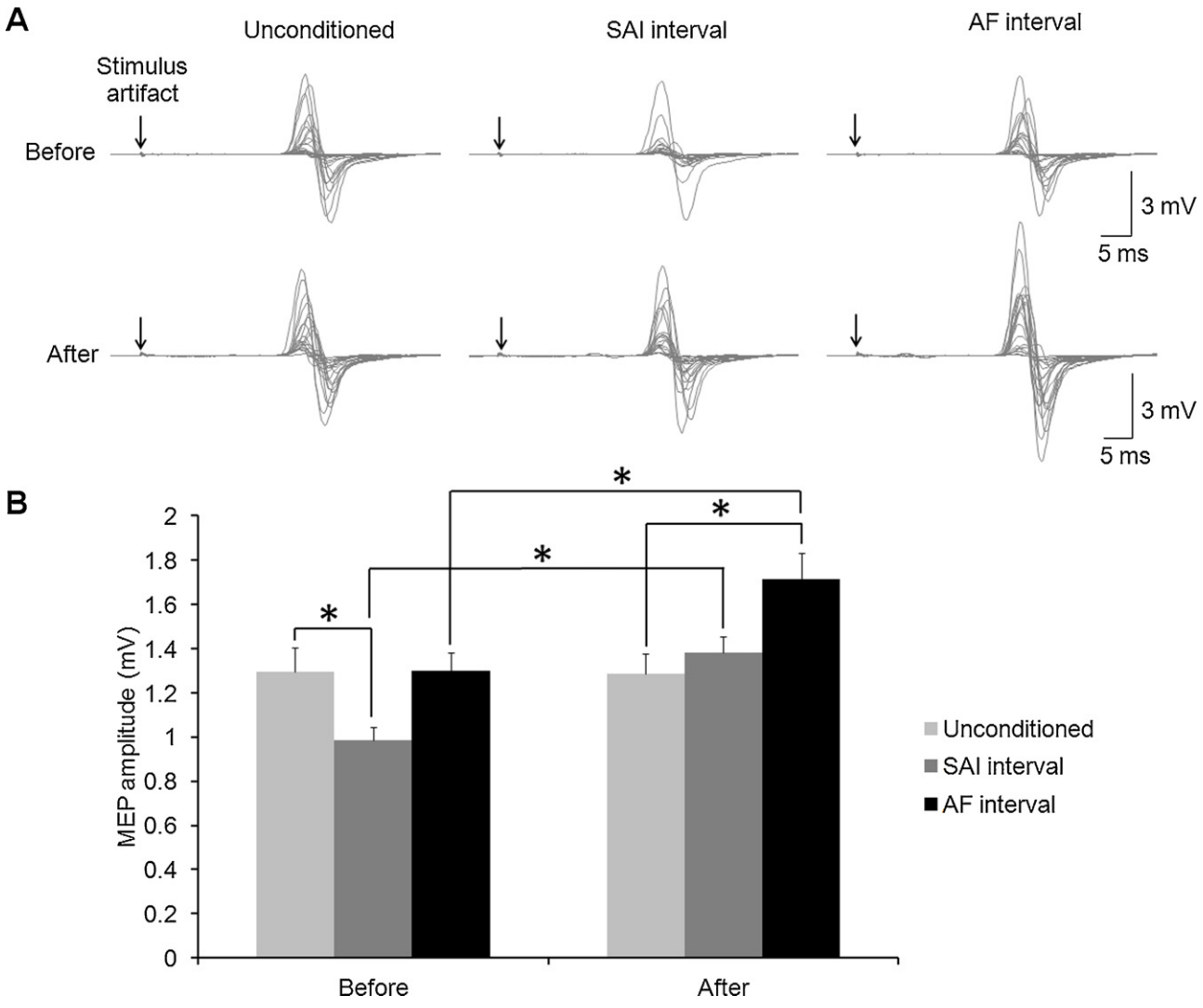

Fig. 2. Amplitude of unconditioned MEPs and MEPs conditioned at SAI and AF C-T intervals before and after a single session of NMES. Panel A shows each MEP waveform (grey lines; $n = 20$) from a single participant recorded before and after NMES. Black arrows indicate the TMS stimulus artifacts. Panel B shows mean amplitudes of MEPs averaged across the group ($n = 9$). Black bars and asterisks indicate comparisons that are significantly different ($p < 0.05$). Error bars represent one standard error.

NMES, conditioned MEPs at both intervals were larger than they were at the comparable intervals before NMES. Also, after NMES, MEPs at the SAI interval were similar in amplitude to unconditioned MEPS and MEPs at the AF interval were larger than unconditioned MEPs.

The amplitudes of unconditioned and conditioned MEPs averaged across all participants before and after NMES are shown in Fig. 2B. There was a significant interaction between "Time" and "Condition" [$F_{(2,16)} = 3.71$, $p = 0.04$]. Post hoc comparisons confirmed that unconditioned MEPs evoked before and after NMES were not different ($p = 0.94$), consistent with the fact that we adjusted stimulus intensity to generate unconditioned MEPs of similar amplitude before and after NMES. The effect of the conditioning stimuli on test MEP amplitude differed before and after NMES. MEPs conditioned using the SAI interval were 25% smaller than unconditioned MEPs before NMES ($p = 0.03$), but were not different than unconditioned MEPs after NMES (8% larger, $p = 0.44$). Further, MEPs conditioned at this interval were 40% larger after NMES than before NMES ($p < 0.01$). The amplitudes of MEPs conditioned using the AF interval were not significantly different than unconditioned MEPs before NMES (0.4% smaller, $p = 0.97$), but were 33% larger than unconditioned MEPs after NMES ($p < 0.01$). Further, the amplitudes of MEPs elicited at this interval were 32% larger after NMES compared to before NMES ($p < 0.01$).

4. Discussion

Changes in excitability of cortical circuits interposed between the ascending afferent volley and descending CS pathways measured in the present study were consistent with the general CS excitability increase induced by NMES. MEPs evoked at 120% of the pre-NMES resting motor threshold were ~1.7 times larger after the NMES than before NMES, confirming that CS excitability was enhanced after NMES. Concurrent with this NMES-induced increase in CS excitability we found that the effect of afferent inputs on inhibitory cortical circuits was reduced; the C-T interval that significantly inhibited test MEPs (SAI) before NMES did not significantly alter MEP amplitude after NMES. Similarly, the effect of afferent inputs on excitatory cortical circuits increased after NMES; the C-T interval used to test these circuits (AF) did not significantly alter test MEPs before NMES, but significantly increased test MEP amplitude after NMES. Thus the present results support our hypothesis that when NMES increases CS excitability, there is a concomitant decrease in SAI and an increase in AF.

NMES-induced increases in CS excitability have been demonstrated in almost every muscle tested thus far [2,10,13,15,18,19,23], with the exception of soleus [14,17]. The specific circuitry involved in CS excitability increases following NMES is not well understood and the locus of the NMES effect is somewhat controversial. Most evidence indicates that NMES increases the excitability of cortical circuits [2,23,26], but there is some evidence for enhanced spinal excitability as well [13,17]. Although beyond the scope of the present study, it is important to note that NMES can be applied with different combinations of stimulation parameters and patterns, and not all combinations have been tested for their effects on cortical versus spinal excitability [4]. To gain a better understanding of the circuitry involved in enhanced CS excitability following the NMES protocol used in the present study, we investigated the effect of NMES on cortical circuitry activated by afferent input from the hand.

Afferent input from a peripheral nerve activates inhibitory and excitatory cortical circuitry. For hand muscles, SAI occurs when a mixed peripheral nerve is stimulated 18–25 ms prior to a magnetic stimulus delivered over M1 [27] and AF occurs at C-T intervals ranging from 25 to 80 ms [5,6]. CS volleys recorded from electrodes implanted in the cervical epidural space suggest that SAI of hand muscles involves cortical, rather than spinal, circuits [27]. Likewise, evidence that AF of MEPs is present when TMS is delivered over M1, but not when delivered over the pyramidal decussation, suggest that AF also involves cortical circuits [24]. Pharmacological studies by Di Lazzaro and colleagues demonstrate that both cholinergic and gamma-amino-butyric acid (GABA)-ergic systems play a role in SAI [7–9]. Scopolamine, an anti-cholinergic drug [7], reduces SAI. Likewise, lorazepam and zolpidem, positive allosteric modulators of the $GABA_A$ receptor, also reduce SAI, possibly through a GABAergic effect on cholinergic function [8,9]. Interestingly, diazepam, another $GABA_A$ receptor agonist, enhanced SAI in one study [8] and had no effect on SAI in another study [9]. To explain the dissociation of $GABA_A$ agonist drug effects on SAI, the authors speculate that SAI is regulated via: (1) an inhibitory SAI circuit that increases SAI by activation of one $GABA_A$ receptor subtype (possibly the α5-subunit) and, (2) another circuit that decreases SAI by control of acetyl-choline release through activation of a different $GABA_A$ receptor subtype [9]. Presently, we found that SAI was abolished concomitant with enhanced CS excitability following NMES, suggesting that decreased sensorimotor inhibition contributed to enhanced CS excitability after NMES. Taken with the work by Di Lazzaro and colleagues [7–9], our findings may provide a clue as to the involvement of specific $GABA_A$ receptor subtypes in NMES-induced increases in CS excitability under the present experimental conditions.

Another explanation for the loss of SAI and emergence of AF following NMES in the present study is that enhanced excitability of pyramidal neurons in M1 following NMES masked SAI and enhanced AF; however, we attempted to minimise this possibility by adjusting the cortical test stimulus intensity to evoke similar amplitude test responses before and after NMES. Further, past work demonstrated that when conventional PAS increased CS excitability, SAI was not affected [26], indicating that changes in SAI concomitant with CS excitability increases are not due solely to enhanced excitability of pyramidal neurons. We propose that, in the present study, NMES altered the excitability of cortical circuits interposed between the ascending afferent volley and the descending CS pathway, which contributed to an increase in CS excitability. Quartarone and colleagues [22] suggest that reduced SAI following high frequency PAS is due to potentiation of a facilitatory sensorimotor pathway distinct from the inhibitory pathways involved in SAI. In this scenario, the enhanced facilitatory sensorimotor drive to the CS motor output neurons would shift the balance between SAI towards AF. This explanation would also be consistent with our finding of a loss of SAI and emergence of AF concomitant with increased CS excitability.

5. Conclusions

The present study demonstrates that when NMES increases CS excitability for FDI, there is a concomitant loss of SAI and emergence of AF of circuits in M1. Thus, reduced activity in inhibitory pathways involved in SAI and enhanced activity of facilitatory pathways involved in AF may contribute to increases in CS excitability evoked by NMES when delivered under the present experimental conditions. The results also indicate that over the course of an NMES session, there is a net increase in the excitatory effect of afferent inputs on cortical circuits. Thus, a given afferent input will have a greater excitatory effect on M1 at the end of a single NMES session than at the beginning. Identifying how best to maximise this excitatory effect of afferent input on M1 circuits may help to strengthen CS pathways and improve functional outcomes of NMES-based rehabilitation programs.

Acknowledgements

This work was supported by a NSERC Canada Graduate Scholarship (CSM), an Alberta Paraplegic Foundation PhD Studentship (AJB), a NSERC Summer Studentship (SMR), and a NSERC Discovery grant (DFC). The authors thank Mr. Alejandro Ley and Mr. Zoltan Kenwell for their technical support.

References

[1] P. Celnik, F. Hummel, M. Harris-Love, R. Wolk, L.G. Cohen, Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke, Archives of Physical Medicine and Rehabilitation 88 (11) (2007) 1369–1376.
[2] C.S. Charlton, M.C. Ridding, P.D. Thompson, T.S. Miles, Prolonged peripheral nerve stimulation induces persistent changes in excitability of human motor cortex, Journal of the Neurological Sciences 208 (1–2) (2003) 79–85.
[3] R. Chen, B. Corwell, M. Hallett, Modulation of motor cortex excitability by median nerve and digit stimulation, Experimental Brain Research 129 (1) (1999) 77–86.
[4] L.S. Chipchase, S.M. Schabrun, P.W. Hodges, Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters, Clinical Neurophysiology 122 (3) (2011) 456–463.
[5] V. Deletis, J.H. Schild, A. Beric, M.R. Dimitrijevic, Facilitation of motor evoked potentials by somatosensory afferent stimulation, Electroencephalography and Clinical Neurophysiology 85 (5) (1992) 302–310.
[6] H. Devanne, A. Degardin, L. Tyvaert, P. Bocquillon, E. Houdayer, A. Manceaux, P. Derambure, F. Cassim, Afferent-induced facilitation of primary motor cortex excitability in the region controlling hand muscles in humans, European Journal of Neuroscience 30 (3) (2009) 439–448.
[7] V. Di Lazzaro, A. Oliviero, P. Profice, M.A. Pennisi, S. Di Giovanni, G. Zito, P. Tonali, J.C. Rothwell, Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex, Experimental Brain Research 135 (4) (2000) 455–461.
[8] V. Di Lazzaro, A. Oliviero, E. Saturno, M. Dileone, F. Pilato, R. Nardone, F. Ranieri, G. Musumeci, T. Fiorilla, P. Tonali, Effects of lorazepam on short latency afferent inhibition and short latency intracortical inhibition in humans, Journal of Physiology 564 (Pt. 2) (2005) 661–668.
[9] V. Di Lazzaro, F. Pilato, M. Dileone, P. Profice, F. Ranieri, V. Ricci, P. Bria, P.A. Tonali, U. Ziemann, Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: a TMS study, Clinical Neurophysiology 118 (10) (2007) 2207–2214.
[10] S. Hamdy, J.C. Rothwell, Q. Aziz, K.D. Singh, D.G. Thompson, Long-term reorganization of human motor cortex driven by short-term sensory stimulation, Nature Neuroscience 1 (1) (1998) 64–68.
[11] L.R. Hoffman, E.C. Field-Fote, Cortical reorganization following bimanual training and somatosensory stimulation in cervical spinal cord injury: a case report, Physical Therapy 87 (2) (2007) 208–223.
[12] A. Kaelin-Lang, A.R. Luft, L. Sawaki, A.H. Burstein, Y.H. Sohn, L.G. Cohen, Modulation of human corticomotor excitability by somatosensory input, Journal of Physiology 540 (Pt. 2) (2002) 623–633.
[13] S. Khaslavskaia, M. Ladouceur, T. Sinkjaer, Increase in tibialis anterior motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve, Experimental Brain Research 145 (3) (2002) 309–315.
[14] T. Kitago, R. Mazzocchio, G. Liuzzi, L.G. Cohen, Modulation of H-reflex excitability by tetanic stimulation, Clinical Neurophysiology 115 (4) (2004) 858–861.

[15] M.E. Knash, A. Kido, M. Gorassini, K.M. Chan, R.B. Stein, Electrical stimulation of the human common peroneal nerve elicits lasting facilitation of cortical motor-evoked potentials, Experimental Brain Research 153 (3) (2003) 366–377.
[16] T. Kujirai, M.D. Caramia, J.C. Rothwell, B.L. Day, P.D. Thompson, A. Ferbert, S. Wroe, P. Asselman, C.D. Marsden, Corticocortical inhibition in human motor cortex, Journal of Physiology 471 (1993) 501–519.
[17] O. Lagerquist, C.S. Mang, D.F. Collins, Changes in spinal but not cortical excitability following combined electrical stimulation of the tibial nerve and voluntary plantar-flexion, Experimental Brain Research 222 (2012) (2012) 41–53.
[18] C.S. Mang, J.M. Clair, D.F. Collins, Neuromuscular electrical stimulation has a global effect on corticospinal excitability for leg muscles and a focused effect for hand muscles, Experimental Brain Research 209 (3) (2011) 355–363.
[19] C.S. Mang, O. Lagerquist, D.F. Collins, Changes in corticospinal excitability evoked by common peroneal nerve stimulation depend on stimulation frequency, Experimental Brain Research 203 (1) (2010) 11–20.
[20] M.N. McDonnell, M.C. Ridding, Afferent stimulation facilitates performance on a novel motor task, Experimental Brain Research 170 (1) (2006) 109–115.
[21] D.R. McKay, M.C. Ridding, P.D. Thompson, T.S. Miles, Induction of persistent changes in the organisation of the human motor cortex, Experimental Brain Research 143 (3) (2002) 342–349.
[22] A. Quartarone, V. Rizzo, S. Bagnato, F. Morgante, A. Sant'Angelo, P. Girlanda, H.R. Siebner, Rapid-rate paired associative stimulation of the median nerve and motor cortex can produce long-lasting changes in motor cortical excitability in humans, Journal of Physiology 575 (Pt. 2) (2006) 657–670.
[23] M.C. Ridding, B. Brouwer, T.S. Miles, J.B. Pitcher, P.D. Thompson, Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects, Experimental Brain Research 131 (1) (2000) 135–143.
[24] F.D. Roy, M.A. Gorassini, Peripheral sensory activation of cortical circuits in the leg motor cortex of man, Journal of Physiology 586 (Pt. 17) (2008) 4091–4105.
[25] H. Russmann, J.C. Lamy, E.A. Shamim, S. Meunier, M. Hallett, Associative plasticity in intracortical inhibitory circuits in human motor cortex, Clinical Neurophysiology 120 (6) (2009) 1204–1212.
[26] K. Stefan, E. Kunesch, R. Benecke, L.G. Cohen, J. Classen, Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation, Journal of Physiology 543 (Pt. 2) (2002) 699–708.
[27] H. Tokimura, V. Di Lazzaro, Y. Tokimura, A. Oliviero, P. Profice, A. Insola, P. Mazzone, P. Tonali, J.C. Rothwell, Short latency inhibition of human hand motor cortex by somatosensory input from the hand, Journal of Physiology 523 (Pt. 2) (2000) 503–513.