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Dissecting the Mechanisms Underlying Short-Interval Intracortical Inhibition Using Exercise

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Recently, 2 physiologically distinct phases of short-interval intracortical inhibition (SICI) have been identified, a larger phase at interstimulus interval (ISI) 3 ms and a smaller phase at ISI 1 ms. While the former is mediated by synaptic processes, the mechanisms underlying the first phase of SICI remain a matter of debate. Separately, it is known that fatiguing hand exercise reduces SICI, a measure of cortical excitability. Consequently, the present study assessed effects of fatiguing hand exercise on the 2 SICI phases, using threshold tracking transcranial magnetic stimulation techniques, to yield further information on underlying mechanisms. Studies were undertaken on 22 subjects, with SICI assessed at baseline, after each voluntary contraction (VC) period of 120 s and 5, 10, and 20 min after last VC, with responses recorded over abductor pollicis brevis. Exercise resulted in significant reduction of SICI at ISI 1 ms ($SICI_{baseline}$ 9.5 ± 2.7%; $SICI_{MAXIMUM\ REDUCTION}$ 2.5 ± 2.5%, $P < 0.05$) and 3 ms ($SICI_{baseline}$ 16.8 ± 1.7%; $SICI_{MAXIMUM\ REDUCTION}$ 11.6 ± 2.1%, $P < 0.05$), with the time course of reduction being different for the 2 phases. Taken together, findings from the present study suggest that synaptic processes were the predominant mechanism underlying the different phases of SICI.

Keywords: motor evoked potential, short interval intracortical inhibition, voluntary contraction

Introduction

Short-interval intracortical inhibition (SICI) has been utilized as a marker of intracortical neuronal processing to interpret function and pathophysiology of neurological diseases (Kujirai et al. 1993; Nakamura et al. 1997; Di Lazzaro et al. 1998a, 1998b; Vucic et al. 2006). More recently, 2 physiologically distinct phases of SICI have been identified, peaking at an interstimulus interval (ISI) of 1 and 2.5–3 ms (Fisher et al. 2002; Roshan et al. 2003; Vucic et al. 2006). While the later peak of SICI (ISI 2.5–3 ms) appears to be mediated by inhibitory γ-aminobutyric acidergic (GABAergic) intracortical circuits, acting via $GABA_A$ receptors (Fisher et al. 2002; Roshan et al. 2003; Ziemann 2004a, 2004b; Vucic, Cheah, Krishnan, et al. 2009), the mechanisms underlying peak SICI at ISI 1 ms remain a matter of debate. Fisher et al. (2002) suggested that relative refractoriness of cortical inhibitory axons mediated inhibition at ISI 1 ms, although it was also acknowledged that postsynaptic potentials evoked by a conditioning and test may summate at short ISIs. Of further relevance, others have argued that synaptic mechanisms, namely a balance between inhibitory and facilitatory processes, solely contribute to the development of SICI at 1 ms (Roshan et al. 2003; Ni and Chen 2008; Peurala et al. 2008).

Physiological and pharmacological factors have been reported to modulate the synaptic processes underlying SICI (Ziemann et al. 1995, 1996a, 1996b; Ziemann and Hallett 2001; Ziemann 2004a; Benwell et al. 2006; Rosenkranz et al. 2007; McNeil et al. 2009; Takahashi et al. 2009). Specifically, some studies have demonstrated a transient reduction in SICI after hand exercise (Maruyama et al. 2006; Takahashi et al. 2009). This reduction in SICI was attributed to a compensatory downregulation of inhibitory cortical processes that developed in response to changes in cortical excitability. Voluntary isometric contraction (VC) may also result in substantial activity-dependent hyperpolarization (ADH) as a consequence of activation of the electrogenic Na^+-K^+ pump, with the degree of hyperpolarisation being greater in peripheral motor axons than cutaneous afferents (Vagg et al. 1998; Kiernan et al. 2004). Of relevance, membrane hyperpolarization may be expected to reduce axonal refractoriness in the peripheral motor axon (Miller et al. 1996; Kiernan and Bostock 2000; Vucic, Krishnan, and Kiernan 2007; Krishnan et al. 2008). Whether the findings of ADH are directly applicable to cortical neuronal axons remain to be determined, although activity-dependent conduction block in central neurons, presumably mediated by ADH, has been reported in multiple sclerosis (van der Kamp et al. 1991; Boniface and Mills 1992; Vucic et al. 2010). Given that relative refractoriness of cortical interneuronal axons may contribute to the generation of SICI at ISI 1 ms (Fisher et al. 2002), the issue of whether voluntary contraction (VC) influences SICI may provide further insights into the mechanisms underlying the different phases of intracortical inhibition.

The different phases of SICI may be assessed using the threshold tracking paired-pulse transcranial magnetic stimulation (TMS) technique, whereby SICI is heralded by greater test stimulus intensity required to produce and maintain a fixed motor evoked potential (MEP) amplitude (Vucic et al. 2006). Consequently, the present study utilized the threshold tracking TMS technique to investigate the effects of fatiguing hand exercise on the different phases of SICI to provide further insights into the mechanisms underlying the generation of SICI at ISI 1 and 3 ms.

Materials and Methods

Studies were undertaken on 22 right-handed healthy volunteers (12 men and 10 women, mean 46 years, age range 23–76 years). None of the subjects had symptoms or clinical signs of central or peripheral nerve dysfunction. Subjects gave written informed consent to the procedures, and all procedures were approved by the South Eastern Sydney Area Health Service Human Research Ethics Committee (Eastern Section).

Peripheral Nerve Studies

Prior to undertaking cortical excitability testing, the median nerve was stimulated electrically at the wrist using a stimulus of 1-ms duration

delivered via 5-mm Ag-AgCl surface electrodes (ConMed). The resultant compound muscle action potential (CMAP) was recorded from the right abductor pollicis brevis (APB) muscle using surface electrodes. The peak-to-peak amplitude and onset latency for the CMAP response were determined. In addition to calculating the CMAP amplitude, the neurophysiological index (NI), a measure of peripheral disease burden, was derived according to a previously reported formula (de Carvalho and Swash 2000):

$$\text{Neurophysiological index} = [\text{CMAP amplitude}/\text{DML}] \times F\text{wave frequency},$$

where *F*-wave frequency refers to the number of *F* responses recorded in 20 trials and DML refers to the distal motor latency. The NI is a marker of peripheral disease burden.

Cortical Excitability

Cortical excitability testing was undertaken by applying TMS to the motor cortex by means of a 90 mm circular coil oriented to induce current flow in a posterior–anterior direction. The coil was adjusted until the optimal position for the MEP was obtained from the APB muscle. Currents were generated by 2 high-power magnetic stimulators that were connected via a BiStim module (Magstim Co.), such that conditioning and test stimuli could be independently set and delivered through 1 coil.

TMS Threshold Tracking

In the conventional paired-pulse technique, the conditioning and test stimuli are kept at constant intensity, and changes in the MEP amplitude are measured. In the present study, the target MEP was of a predetermined fixed amplitude and changes in the test stimulus intensity required to generate this target response, when preceded by a subthreshold conditioning stimulus, were measured (Vucic et al. 2006). The threshold tracking strategy used a target response of 0.2 mV (±20%) as described previously (Fisher et al. 2002; Vucic et al. 2006). Resting motor threshold (RMT) was defined as the stimulus intensity required to produce and maintain this target MEP response.

Experimental Design

Subjects performed 3 VC contractions of the APB muscle (Fig. 1*A*). All subjects were seated in a comfortable chair in front of a projector and instructed to abduct their thumb against a force transducer without flexing the wrist. Visual feedback was provided about the level of force produced, and subjects were encouraged to maintain maximal contraction for 120 s. Each contraction lasted for 120 s, and TMS was performed in between each contraction. TMS was performed immediately after the last contraction period and at the following intervals: 5 min after last VC; 10 min after last VC; and 20 min after last VC. The TMS studies lasted for 2 min. The force generated during VC was measured by a strain gage type transducer (XTRAN load cell K4; Applied Measurements), amplified (AMA-RM-044-Singla conditioning unit; Applied Measurements) and passed via a CED 1401 laboratory interface (CED) to a computer for off-line analysis.

Assessing the Effects of Fatigue on Cortical Processes

In order to assess the impact of fatiguing exercise on SICI, a paired-pulse paradigm was used according to a previously devised protocol (Vucic et al. 2006). Subthreshold conditioning stimuli (CS 70% RMT) were delivered in a sequential order to assess SICI at ISIs of 1 and 3 ms. The CS intensity was determined by the evolving rather than baseline RMT. ISIs of 1 and 3 ms values were chosen since peak SICI occurs at these 2 time intervals, and the mechanisms underlying the generation of SICI at these 2 time point remains to be clarified (Fisher et al. 2002; Roshan et al. 2003; Vucic et al. 2006; Vucic, Cheah, Krishnan, et al. 2009). Measurements of SICI and RMT were undertaken at baseline, immediately after each contraction period and 5, 10, and 20 min after cessation of the last contraction period (Fig. 1). Stimuli were delivered in a recurring sequence of: channel 1 tracked the stimulus intensity required to produce the unconditioned test response (i.e., RMT); channel 2 tracked the stimulus required to produce the target MEP when conditioned by a stimulus equal in intensity to that on channel 2. Stimuli were delivered every 5–10 s (stimulus delivery was limited by the charging capability of the BiStim system) and the computer advanced to the next ISI when the tracked MEP was stable.

During the same sitting, MEP amplitude was determined at an intensity of 140% RMT, again referenced to evolving rather than baseline RMT. Three stimuli were delivered at this stimulus intensity, and the mean maximal peak-peak MEP amplitude (mV) and onset latency (ms) were recorded. The MEP was recorded at the same time points as SICI (Fig. 1). Central motor conduction time (CMCT, ms) was calculated using the *F*-wave method and the following formula (Rossini et al. 1985; Mills and Murray 1986; Garassus et al. 1993):

$$\text{CMCT} = \text{MEP latency} - [\text{DML} + F_{\text{min}} - 1]/2,$$

where DML represents the distal motor latency and F_{min} the minimal *F*-wave latency.

Data Analysis

All CMAP and MEP recordings were amplified and filtered (3 Hz–3 kHz) using a Grass ICP511 AC amplifier (Grass-Telefactor, Astro-Med Inc.) and sampled at 10 kHz using a 12-bit data acquisition card (National Instruments PCI-MIO-16E-4). Data acquisition and stimulus delivery (both electrical and magnetic) were controlled by QTRACS software (Institute of Neurology).

Intracortical inhibition, induced by a conditioning stimulus, was measured as the increase in the test stimulus intensity required to

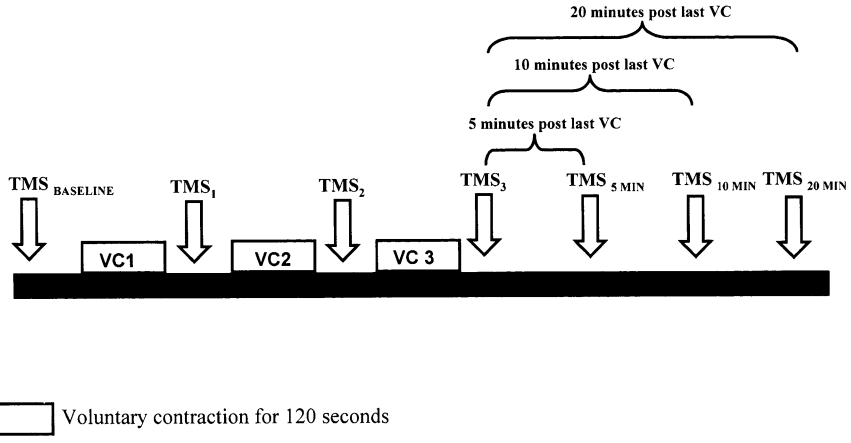

Figure 1. Experimental protocol: TMS was performed at baseline and after each period of VC. In total, there were 3 VC periods, each lasting 120 s. TMS was subsequently performed after 5 (TMS $_{5\ min}$), 10 (TMS $_{10\ min}$), and 20 (TMS $_{20\ min}$) min after the last contraction period.

evoke the target MEP. Inhibition was calculated off-line using the following formula (Fisher et al. 2002; Vucic et al. 2006):

$$\text{Inhibition} = [\text{Conditioned test stimulus intensity} - \text{RMT}]/[\text{RMT} \times 100].$$

Facilitation was measured as the decrease in the conditioned test stimulus intensity required to evoke the target MEP.

Each data point was weighted (by the QTRACS software) such that any measures recorded outside the threshold target window, defined as values within 20% of the tracking target of 0.2 mV (peak-to-peak), contributed least to the data analysis.

Statistical Analysis

All results are expressed as mean ± standard error of the mean. Student's *t*-test was used to assess differences between means. One-way analysis of variance (ANOVA) was used for comparing cortical excitability changes across different time points, with "time point" used as a factor. Post hoc analysis using a Bonferroni correction was utilized for multiple comparisons. A probability (P) value of <0.05 was considered statistically significant. Although an attempt was made to control for multiple comparisons, a conservative interpretation of the results may seem warranted, given that multiple comparisons were undertaken.

Results

A complete sequence of recordings was obtained from all subjects. The mean duration of TMS testing for each period, and thereby the time interval between each VC period, was 2.6 ± 0.2 min. Furthermore, on average 25 ± 1 stimuli were delivered during each TMS testing period. The peak-to-peak CMAP amplitude was 9.4 ± 0.8 mV, while the NI was 2.4 ± 0.2, both within the previously reported normal range (Vucic et al. 2006; Vucic, Cheah, Krishnan, et al. 2009). In addition, the mean median nerve distal motor latency was 3.9 ± 0.1 ms, while the minimal *F*-wave latency was 29.3 ± 0.6 ms, both within previously established control ranges (Vucic et al. 2006; Vucic, Cheah, Krishnan, et al. 2009). There was a reduction in mean peak force generated by thumb abduction from 34.3 ± 4.0 N (first contraction period) to 29.3 ± 3.2 N (second contraction period) and 24.7 ± 2.6 N (third period), although this reduction was not significant (ANOVA $F = 1.0$, $P = 0.36$).

Effects of Fatiguing Exercise on Cortical Processes

In order to assess the effects of fatiguing exercise on cortical processes, SICI was measured at an ISI of 1 and 3 ms. These 2 time points were selected based on previous data demonstrating that SICI exhibits 2 peaks, a smaller peak at ISI 1 ms and a larger peak at 3 ms (Vucic et al. 2006). At baseline, SICI at ISI 1 ms was 9.5 ± 2.7%. With VC, there was a significant reduction of SICI at ISI 1 ms, peaking 5 min after the last VC period ($SICI_{1\ ms}$ 2.5 ± 2.5%, ANOVA, $F = 6.0$, $P < 0.05$, Fig. 2). By the time of final testing, 20 min after the last VC period, SICI had returned to baseline ($SICI_{1\ ms}$ at 20 min 9.2 ± 2.9%).

In the same sitting, SICI was assessed at ISI of 3 ms. At baseline, SICI at ISI 3 ms was 16.8 ± 1.7% and was significantly greater than SICI at ISI 1 ms ($P < 0.05$). There was a significant reduction in SICI at ISI 3 ms, peaking immediately after the end of the second VC period ($SICI_{3\ ms}$ 11.6 ± 2.1%, ANOVA, $F = 4.8$, $P < 0.05$, Fig. 3*A*). At final testing, 20 min after the last VC, SICI at ISI 3 ms had normalized ($SICI_{1\ ms}$ at 20 min 16.1 ± 2.3%). The mean SICI reduction at ISI 1 ms (−7.1 ± 2.3%) was comparable with SICI reduction at ISI 3 ms (−5.0 ± 1.9%, $P = 0.25$).

In addition to SICI, the MEP amplitude, expressed as a percentage of the CMAP response, was assessed in the same sitting. At baseline, MEP amplitude was 19.9 ± 2.8%. Although MEP amplitude reduced with fatiguing exercise, with peak reduction occurring after the first contraction period (15.6 ± 2.0%), this reduction was not significant (ANOVA, $F = 0.64$, $P = 0.7$) and remained unchanged throughout the testing and

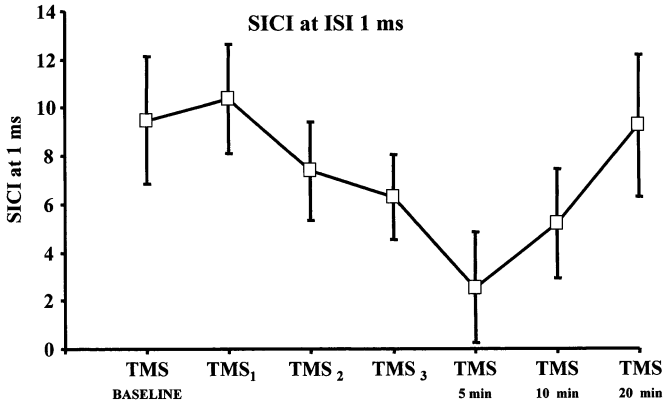

Figure 2. The effects of fatiguing hand exercise on SICI at an ISI of 1 ms were assessed using the threshold tracking TMS technique. There was significant reduction of SICI at ISI 1 ms, peaking 5 min after the last VC period (TMS 5 min).

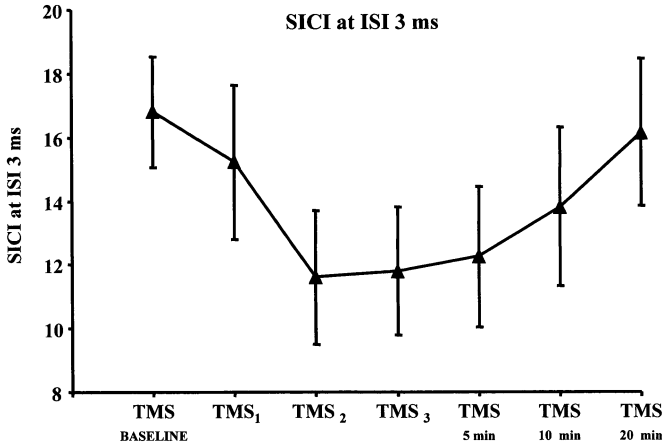

Figure 3. (*A*) The effects of fatiguing hand exercise on SICI at an ISI of 3 ms were assessed using the threshold tracking TMS technique. There was significant reduction of SICI at ISI 3 ms, peaking after the end of the second VC period (TMS 2).

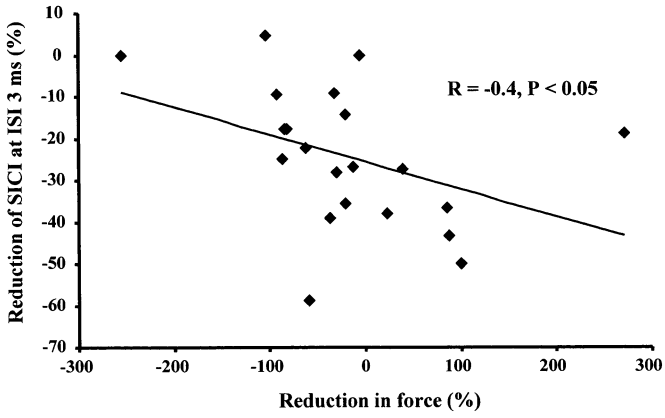

Figure 4. The reduction of SICI at ISI 3 ms significantly correlated with the reduction in force generated by thumb abduction.

recovery periods (MEP amplitude 20 min post last VC 18.1 ± 1.9%).

The effects of fatiguing exercise on the MEP latency and CMCT were also assessed. At baseline, MEP latency (21.6 ± 0.6 ms) and CMCT (5.5 ± 0.5 ms) were comparable with previously reported values (Vucic et al. 2006; Vucic, Cheah, Krishnan, et al. 2009). There were no significant changes in the MEP latency (21.9 ± 0.5 ms) and CMCT (5.8 ± 0.4 ms) during fatiguing exercise. RMT at baseline was 54.4 ± 1.9%, and there was no significant change in the RMT following fatiguing exercise (TMS1 53.4%; TMS2 54%; TMS3 54.1%; TMS 5 min 53.5%; TMS 10 min 53.4%; TMS 20 min 53.3%, $F = 0.03$, $P = 1.0$).

Mechanisms Underlying Different Phases of SICI

Correlation studies were undertaken to assess whether SICI at 1 and 3 ms was mediated by similar cortical circuits and whether the reduction of SICI correlated with force generated by thumb abduction. There was a significant correlation between maximal reduction in SICI at ISI 3 ms and the decline in force generated by thumb abduction ($R = -0.4$, $P < 0.05$, Fig. 4). In contrast, there was no significant correlation between SICI reduction at 1 ms and the force generated by thumb abduction ($R = -0.2$, $P = 0.2$), as there was no correlation between maximal SICI reduction at 1 and 3 ms ($R = -0.1$, $P = 0.4$). Furthermore, baseline SICI at ISI 1 ms did not correlate with baseline SICI at 3 ms ($R = 0.3$, $P = 0.2$). Taken together, these findings may suggest that different cortical circuits contribute to the development of SICI at ISI 1 and 3 ms and that SICI reduction, in particular at ISI 3 ms, may represent a compensatory downregulation of intracortical inhibition, acting to maintain cortical output.

Discussion

Using novel threshold tracking TMS techniques, the present study investigated the effects of fatiguing hand exercise on different phases of cortical excitability to help clarify the mechanisms underlying the generation of SICI. Fatiguing hand exercise resulted in a significant reduction of SICI at ISIs of 1 and 3 ms, although the time course of SICI reduction was different for the 2 phases of SICI. Interestingly, the extent of SICI reduction at ISI 3 ms correlated with the decline in force generated by thumb abduction. As such, the combined findings may suggest that the 2 peaks of SICI are mediated by synaptic mechanisms, perhaps through different cortical circuits. Of further relevance, fatiguing hand exercise is associated with downregulation of inhibitory cortical processes, which appear to be important in maintaining the force output from the contralateral limb. The mechanisms underlying these findings and their potential clinical implications will form the basis of the discussion.

Mechanisms Underlying the Generation of SICI

It is now accepted that the second phase of SICI is synaptic in origin, mediated by GABAergic inhibitory neurons acting via $GABA_A$ receptors (Kujirai et al. 1993; Ziemann et al. 1996a, 1996b; Muller-Dahlhaus et al. 2008; Vucic, Cheah, Krishnan, et al. 2009). Evidence supporting synaptic mechanisms was provided by epidural recordings in which descending cortico-motoneuronal volleys were inhibited during SICI (Nakamura et al. 1997; Di Lazzaro et al. 1998b; Hanajima et al. 1998). Combined with PET studies that revealed changes in cerebral blood flow in the motor cortex with paired-pulse TMS studies (Strafella and Paus 2001).

The mechanisms underlying the reduction of SICI after VC remain to be determined, although probably represent a transient compensatory downregulation of inhibitory processes, attempting to maintain cortical output (Maruyama et al. 2006). Given that GABAergic intracortical inhibitory circuits underlie the generation of SICI, the observed findings may reflect a transient downregulation or weakening (long-term depression, LTD) of preexisting synaptic processes, as reported with transient muscle ischemia and low-frequency repetitive TMS (Ziemann et al. 1998). Of particular relevance, LTD may have contributed to reduction of SICI at 3 ms, above and beyond the reduction of SICI at ISI 1 ms, since SICI was studied using a fixed rather than random order of ISIs. Interestingly, the GABAergic inhibitory circuits normally receive facilitatory input that may be downregulated after VC, further contributing to SICI reduction observed in the present study (Maruyama et al. 2006). However, reduction in SICI may have resulted from reduction in the MEP amplitude, as was reported in previous studies (Chen et al. 1998; Maruyama et al. 2006). Given that a fixed MEP amplitude was tracked in the present study and that the MEP amplitude did not significantly decline after VC, these findings argue against a significant contribution of changes in MEP amplitude to the observed reduction in SICI.

Reduction of SICI at ISI 1 ms

Potential mechanisms underlying the first phase of SICI remain a matter of debate. While some have proposed that this initial phase of SICI may be mediated by refractoriness of cortical interneuronal axons (Fisher et al. 2002), others have suggested that synaptic mechanisms are solely responsible for generation of this initial phase of SICI (Roshan et al. 2003). Previously, our findings have also suggested that synaptic processes appeared the dominant mechanism in the generation of SICI at ISI 1 ms, although a contribution from axonal refractoriness of cortical interneurons could not be excluded (Vucic, Cheah, Krishnan, et al. 2009). Findings from the present study, specifically that both phases of SICI were significantly reduced by fatiguing exercise, provides further supportive evidence that synaptic processes mediate SICI reduction at ISI 1 ms. Absence of significant correlation between the 2 SICI phases, and the differing time course in SICI reduction, suggest that different inhibitory cortical circuits were responsible for the generation of the 2 SICI peaks.

A potential limitation of this study was that a relative contribution of changes in peripheral nerve excitability post-VC was not formally assessed. Specifically, VC induces ADH, and thereby increases threshold to activation, which is more prominent in motor axons (Vagg et al. 1998; Kiernan et al. 2004). Although unlikely, the possibility that changes in peripheral nerve excitability contributed to the observed reduction in motor cortex excitability cannot be absolutely discounted.

Clinical Implications

The development of cortical hyperexcitability, as reflected by reduction of SICI, has been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS), a rapidly progressive neurodegenerative disorder of motor neurons (Ziemann et al. 1997; Zanette et al. 2002; Winhammar et al. 2005; Vucic and

Kiernan 2006, 2007, 2009; Vucic, Burke, and Kiernan 2007; Vucic et al. 2008; Vucic, Cheah, and Kiernan 2009). Furthermore, high-intensity exercise has been identified as a potential risk factor for ALS (Chio et al. 2005). The pathophysiological link between exercise and the development of ALS remains obscure, although glutamate excitotoxicity may accompany normal motor neurone activation (Kiernan 2009a, 2009b). Findings from the present study demonstrating that fatiguing hand exercise induces changes in cortical excitability may suggest a potential pathophysiological link between ALS and fatiguing exercise. Clarification of a link between exercise and development of cortical hyperexcitability in ALS patients may have implications for future treatment approaches and also in the provision of advice on the safe level of exercise and activity for patients with ALS.

Fatigue is a common symptom in ALS (Sanjak et al. 2001; Thomas and Zijdewind 2006). The mechanisms underlying fatigue in ALS are complex, and contributions from both central and peripheral nervous systems have been reported (Sanjak et al. 2001; Vucic, Krishnan, and Kiernan 2007). Central fatigue refers to reduced excitatory drive to motor neurons, secondary to central nervous system dysfunction, resulting in incomplete motor unit recruitment (Carpentier et al. 2001; Thomas and Zijdewind 2006; Vucic et al. 2010). Given that fatiguing hand exercise affects cortical processes in healthy controls, studies in ALS patients may yet prove useful in determining the mechanisms of fatigue in ALS that in turn may have therapeutic significance.

In conclusion, using the threshold tracking TMS technique, the present study has established that fatiguing hand exercise reduces SICI at ISI 1 and 3 ms, although the time course of reduction was different for the 2 phases of SICI. Taken together, findings from the present study suggest that synaptic mechanisms underlie the development of both phases of SICI.

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Notes

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