Late Cortical Disinhibition in Human Motor Cortex: A Triple-Pulse Transcranial Magnetic Stimulation Study

R. F. H. Cash,1 U. Ziemann,3 K. Murray,2 and G. W. Thickbroom1

1Centre for Neuromuscular and Neurological Disorders and 2School of Mathematics and Statistics, University of Western Australia, Crawley, Perth, Australia; and 3Department of Neurology, Goethe-University of Frankfurt, Frankfurt, Germany

Submitted 1 July 2009; accepted in final form 12 November 2009

Cash RFH, Ziemann U, Murray K, Thickbroom GW. Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. J Neurophysiol 103: 511–518, 2010. First published November 18, 2009; doi:10.1152/jn.00782.2009. In human motor cortex transcranial magnetic stimulation (TMS) has been used to identify short-interval intracortical inhibition (SICI) corresponding to γ-aminobutyric acid type A (GABA_A) effects and long-interval intracortical inhibition (LICI) and the cortical silent period (SP) corresponding to postsynaptic GABA_B effects. Presynaptic GABA_B effects, corresponding to disinhibition, can also be identified with TMS and have been shown to be acting during LICI by measuring SICI after a suprathreshold priming stimulus (PS). The duration of disinhibition is not certain and, guided by studies in experimental preparations, we hypothesized that it may be longer-lasting than postsynaptic inhibition, leading to a period of late cortical disinhibition and consequently a net increase in corticospinal excitability. We tested this first by measuring the motor-evoked potential (MEP) to a test stimulus (TS), delivered after a PS at interpulse intervals (IPIs) ≤300 ms that encompassed the period of PS-induced LICI and its aftermath. MEP amplitude was initially decreased, but then increased at IPIs of 190–210 ms, reaching 160 ± 17% of baseline 200 ms after PS (P < 0.05). SP duration was 181 ± 5 ms. A second experiment established that the onset of the later period of increased excitability correlated with PS intensity (r² = 0.99) and with the duration of the SP (r² = 0.99). The third and main experiment demonstrated that SICI was significantly reduced in strength at all IPIs ≤220 ms after PS. We conclude that TMS-induced LICI is associated with a period of disinhibition that is at first masked by LICI, but that outlasts LICI and gives rise to a period during which disinhibition predominates and net excitability is raised. Identification of this late period of disinhibition in human motor cortex may provide an opportunity to explore or modulate the behavior of excitatory networks at a time when inhibitory effects are restrained.

INTRODUCTION

A single pulse of transcranial magnetic stimulation (TMS) over motor cortex can elicit multiple excitatory and inhibitory effects over timescales much longer than that of the stimulus itself. For example, the motor-evoked potential (MEP) primarily arises from transynaptic activation of excitatory interneurons at high frequency (~1.5-ms periodicity) for a brief period (~10 ms) (Di Lazzaro et al. 2008; Ziemann and Rothwell 2000). Interactions between these transynaptic events can be observed as short-interval cortical facilitation (SICF) and longer-duration excitatory effects manifest as a later period of intracortical facilitation (ICF) at 8–30 ms (Kujirai et al. 1993; Ziemann et al. 1996b). Inhibitory effects include a short (~10 ms) period of cortical inhibition (short-interval intracortical inhibition [SICI]) mediated through GABAergic interneurons targeting postsynaptic γ-aminobutyric acid type A (GABA_A) receptors (Di Lazzaro et al. 2000, 2006; Hanajima et al. 1998; Kujirai et al. 1993; Ziemann et al. 1993a) and a longer period of up to about 150 ms mediated via postsynaptic GABA_B receptors (long-interval intracortical inhibition [LICI]) (McDonnell et al. 2006; Muller-Dahlhaus et al. 2008; Valls-Sole et al. 1992).

Progress toward unraveling these components and their interrelationships has been possible using purpose-designed TMS protocols and pharmacological studies (for reviews see Paulus et al. 2008; Reis et al. 2008). These studies have revealed interactions between mechanisms that may compete or cooperate for the final outcome. For example, in interactions between excitatory and inhibitory circuits, it has been shown that ICF and SICI superimpose, but that ICF dominates in the later phase of SICI (Ziemann et al. 1996b), and competition between SICI and SICF can occur at I-wave intervals, most notably around 3 ms (Peurula et al. 2008).

Competition may also arise within inhibitory circuits themselves. Activation of the neuronal circuits responsible for LICI also reduces SICI and it has been suggested that this arises from disinhibition through activation of presynaptic GABA_B receptors located on inhibitory interneurons that limit further GABA release (Sanger et al. 2001). The time course over which disinhibition acts in the human is not certain, although there is recent evidence that it differs from that of postsynaptic inhibition (Chu et al. 2008), and experimental cellular studies indicate that presynaptic inhibition can outlast that of postsynaptic GABA_B-receptor activation (Deisz 1999; Otis et al. 1993).

The excitatory and inhibitory properties of human motor cortex in the period following LICI have not been systematically explored. However, if disinhibition does persist, then a post-LICI period of prevailing disinhibition should be present during which a net increase in corticospinal excitability would be anticipated. Two studies have suggested that this might be the case. Valls-Sole et al. (1992) referred to an occasional phase of facilitation occurring later than 200 ms and Wassermann et al. (1996) reported a tendency for facilitation around this time. However, neither of these studies was able to show a statistically significant effect and the phenomenon was not investigated further.

In the present study we have explored in detail the time course of excitation and inhibition during and beyond the period of LICI. We used the amplitude of the motor-evoked potential (MEP) as an index of net corticospinal excitability, a reduction in the strength of SICI as a measure of disinhibition (Chu et al. 2008; Sanger et al. 2001), and the strength and duration of LICI and the duration...
of the cortical silent period (SP) as measures of postsynaptic inhibition. We hypothesized that disinhibition would be prolonged compared with inhibition, leading to a period during which disinhibition prevails. The significance of such a period may be the potential for TMS protocols to be applied in an environment of reduced inhibitory effectiveness.

**Methods**

**Subjects**

In all, 18 subjects were recruited for the study. All subjects were healthy and right handed, gave informed written consent, and completed a safety questionnaire prior to the study that had the approval of the local Ethics Committee and conformed to the Declaration of Helsinki. Subjects were seated comfortably with arms resting on a cushion and were asked to remain relaxed but alert with eyes open for the duration of the experiment.

**TMS**

MEPs were recorded from surface electrodes placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) muscle of the right hand. TMS was performed using two or three linked magnetic stimulators (Magstim, Whitland, South West Wales, UK) connected to a 7-cm figure-of-eight coil, placed over the optimal scalp position (determined from initial exploration) for the hand area of the left motor cortex, and orientated about 45° to the sagittal plane so that the induced monophasic current in the brain was directed from lateral-posterior to medial-anterior.

Resting motor threshold (RMT) at the optimal scalp position was defined as the lowest stimulating intensity eliciting MEPs >50 μV peak-to-peak amplitude in at least 5 of 10 trials. Active motor threshold (AMT) was determined during low-level isometric contraction (~20% maximum voluntary contraction [MVC]) and defined as the lowest intensity that elicited a MEP >100 μV in the curve average of 5 consecutive trials. SP recordings were made during a low-level isometric contraction (~20% of MVC) of the right FDI. All other measurements were taken at rest.

**Experiment 1: double-pulse TMS**

A paired-pulse paradigm was used in which a suprathreshold priming stimulus (PS) was followed by a test stimulus (TS) to probe LICI as well as the period immediately following LICI (Table 1). Eleven subjects (six female; 19–36 yr of age) were recruited for this experiment. The intensity of PS was set to give a MEP of about 1 mV in peak-to-peak amplitude (~1.25 × RMT). TS intensity was set equal to PS. Paired-pulse TMS (PS–TS) was delivered every 5 s at nine interpulse intervals (IPIs) in the range 100–270 ms (specifically: 100, 150, 170, 190, 200, 210, 230, 250, and 270 ms). Each interval was repeated pseudorandomly six times. Because PS and TS intensity were equal, the mean amplitude (across all IPIs) of the MEP to the PS served as the unconditioned control. SP measurements were taken during a low-level voluntary contraction at this PS intensity and SP duration was censored from the onset of the PS MEP until the return of electromyographic activity. Peak-to-peak amplitude of the TS MEP was averaged for each IPI and expressed as a percentage of the mean PS MEP.

**Experiment 2: effect of PS intensity**

In a subset of nine subjects (five female; 19–36 yr of age), the effect of PS intensity was examined, at levels of 1.1, 1.2, and 1.3 × RMT at the same IPIs as for **experiment 1** (Table 1). In five of these subjects who had a relatively low threshold, it was also possible to make recordings at 1.4 × RMT. SP duration was determined at these same intensities.

**Experiment 3: triple-pulse TMS**

To measure SICI during and after LICI, a triple-pulse paradigm was used, in which a paired condition–test stimulus (CS/TS) combination, typically used to measure SICI, was delivered at various times after the PS (Table 1). Seven additional subjects (three female; 19–38 yr of age) participated in this experiment, which included a replication of **experiment 1**. An interval of 2 ms was selected as the CS/TS interval because, at this interval and with subthreshold CS intensity, SICI is not contaminated by SICF (Peurala et al. 2008). As previously, PS intensity was set to give a MEP of about 1 mV in amplitude (~1.25 × RMT). For TS intensity, we followed an adjustment protocol described in Sanger et al. (2001) and Chu et al. (2008); at each IPI, a PS–TS combination was delivered and TS intensity adjusted (TS*) to give a MEP of about 1 mV during coapplication of PS (mean of 10 trials). CS intensity was set at baseline (in the absence of PS) using a TS intensity giving about 1-mV MEP and with CS adjusted to result in roughly 50% attenuation of the TS MEP (i.e., 50% SICI). A range of CS intensities was scanned (from 0.5 to 1.2 × AMT, 7 trials per condition) to determine an appropriate intensity, which was then confirmed with a further run of 10 trials and was, on average, 0.9 × AMT (equivalent to ~0.7 × RMT). The value of 50% SICI was selected to avoid floor effects and keep the SICI measurement sensitive to changes induced by PS (cf. Peurala et al. 2008).

Double-pulse (PS–TS*) or triple-pulse (PS–CS/TS*) combinations were delivered at IPIs (interval between PS and TS*) ranging from 100 to 300 ms (10 repeats for each IPI and combination; randomized; IPIs of 100, 150, 175, 190, 200, 210, 220, 250, and 300 ms). At each IPI after the PS, SICI was calculated from the ratio (expressed as a percentage) of the TS* MEP amplitude in the triple-pulse combination (i.e., PS and CS precede TS*) compared to that in the double-pulse combination (i.e., PS precedes TS*). Measurements of SICI in the absence of PS were made throughout the experiment using double-pulse measurements (CS precedes TS) using unadjusted TS intensity and the mean across these measurements served as the reference (unprimed) value for SICI.

**Data analysis**

Results are expressed as means ± SE. A linear mixed model approach was used to determine the effects of fixed factor(s) on each response variable and allowing for a random-effects factor for the individual (subjects). For IPI curves, estimated mean response values at each IPI were compared with baseline control (100%). For the comparison of primed SICI with unprimed SICI, the estimated mean response of primed SICI at each IPI was compared with the average of the unprimed SICI recorded across all IPIs (averaged after confirming no relationship to IPI with a one-way repeated-measures ANOVA). Where the model assumptions were not met, a log or square root transformation of the response was undertaken and analysis was carried out on the transformed response variable.

To enable comparison of the effects of changing PS intensity, the data were fit to a sigmoid curve given by y(x) = a/(1 + be−c·x), where x is IPI in ms; y is normalized (% MEP amplitude); and a, b, and c are the parameters of the curve fit. These curves enabled estimation of the magnitude of MEP facilitation (from parameter a) and the transition between inhibition and facilitation [estimated from the inflection point when y(x0) = a/2, given by x0 = −1/c × ln (1/b)]. Linear regression (Pearson’s correlation coefficient) was applied to inflection point versus SP duration across PS intensity.

**Results**

**Experiment 1: double-pulse TMS**

Figure 1 summarizes the paired-pulse data and shows two phases: initially TS MEP amplitude was reduced after the PS (compared with single-pulse baseline), but then facili-
MEP amplitude had returned to baseline by 270 ms post-PS. The first phase was expected and corresponds to a reduction in MEP amplitude normally associated with LICI. The strongest reduction in MEP amplitude occurred at an IPI of 100 ms (37\% of baseline; \( P < 0.01 \)), but amplitude remained reduced at 150 ms (55\% of baseline; \( P < 0.01 \)). MEP amplitude briefly returned to within baseline values at an IPI of about 180 ms, which was of a similar timing to the mean duration of the SP (181 ± 5 ms). This was followed by a period of MEP facilitation that was significant for IPIs of 190, 200, and 210 ms (143\%, 160\%, and 154\% of baseline, respectively; \( P < 0.05 \)).

**Table 1. Experimental protocols and measures**

<table>
<thead>
<tr>
<th>Description</th>
<th>Stimulus Pattern</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 Unprimed TS (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primed TS</td>
<td></td>
<td>PS TS</td>
</tr>
<tr>
<td>Silent period</td>
<td></td>
<td>Silent period duration (ms)</td>
</tr>
<tr>
<td>E2 Unprimed TS (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primed TS with varied PS</td>
<td></td>
<td>PS TS</td>
</tr>
<tr>
<td>PS intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent period with PS</td>
<td></td>
<td>Silent period duration (ms)</td>
</tr>
<tr>
<td>varied PS intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3 Unprimed TS (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioned TS (CS-TS = 2ms)</td>
<td></td>
<td>CS TS</td>
</tr>
<tr>
<td>Primed TS* (TS* adjusted to 1mV)</td>
<td></td>
<td>PS CS TS*</td>
</tr>
</tbody>
</table>

TS, test stimulus; PS, priming stimulus; CS, conditioning stimulus; TS*, adjusted TS (1 mV); SICI, short-interval intracortical inhibition. Experiment 1 (E1): double-pulse primed inhibition and and excitation; experiment 2 (E2): effect of priming stimulus intensity; experiment 3 (E3): effect of priming on SICI.
Experiment 2: effect of PS intensity

With increasing PS intensity a similar pattern of reduction and facilitation of MEP amplitude was observed (Fig. 2). The data were fit to a sigmoid curve at each PS intensity with high correlation ($r^2$ in the range 0.904–0.974). As PS intensity increased (1.1–1.4 × RMT), the amplitude parameter (a) increased (132, 143, 159, and 271%, respectively) as did the timing of the inflection point (163, 173, 188, and 199 ms, respectively). SP duration at 1.1, 1.2, 1.3, and 1.4 × RMT was 149 ± 9, 174 ± 4, 197 ± 9, and 220 ± 20 ms, respectively, and was correlated with the time of inflection ($r^2 = 0.99$) and PS intensity ($r^2 = 0.99$).

Experiment 3: triple-pulse TMS

First, the PS–TS pattern described in the previous section was confirmed in this subject group. TS MEP amplitude after a PS was significantly reduced at IPIs of 100–175 ms ($P < 0.01$) and facilitated at IPIs of 210 and 220 ms (138 ± 16 and 148 ± 27% baseline; $P < 0.05$).

The reference (unprimed) value for SICI was 53 ± 2%, which did not vary across IPI ($P = 0.34$). The mean (unprimed) TS MEP amplitude was 1.24 ± 0.1 mV and mean adjusted (primed by PS) TS MEP amplitude was 1.21 ± 0.03 mV. With triple-pulse stimulation (measuring SICI after PS), SICI was reduced in strength (compared with

![FIG. 1. Time course of motor-evoked potential (MEP) amplitude change after priming stimulus (PS). A: mean test stimulus (TS) MEP amplitude (% of unconditioned baseline) as a function of interpulse interval (IPI) after PS. An initial period (from 100 to about 175 ms IPI), in which TS amplitude is decreased, is followed by a period of facilitation from 190 to about 230 ms ($*P < 0.05$; $**P < 0.01$). B: example TS MEP waveforms at IPIs after PS (one typical subject; gray MEP and gray bar indicate unprimed TS MEP amplitude).](http://jn.physiology.org/content/103/1/514/F1)

![FIG. 2. Effect of PS intensity. TS MEP amplitude as a function of IPI for 4 PS intensities: 1.1, 1.2, 1.3, and 1.4 × resting motor threshold (RMT). A sigmoid curve has been fit to the data as described in METHODS. Increasing PS intensity increased the initial inhibition, increased the magnitude of the facilitatory period, and delayed the inflection point (transition from inhibition to facilitation). The silent period (SP) duration was correlated with the inflection point and PS intensity (insets).](http://jn.physiology.org/content/103/1/514/F2)
reference level) at all IPIs ≤220 ms (83 ± 13, 85 ± 14,
104 ± 10, 84 ± 7, 82 ± 17, 85 ± 22, and 74 ± 12%; P < 0.05), spanning both phases of MEP amplitude change (inhibition and facilitation) in the paired-pulse recordings
(Fig. 3, cf. Fig. 1). SICI returned to the reference level at an IPI of 250 ms (54 ± 7%).

**Discussion**

The present findings are consistent with previous reports that SICI is reduced during the action of LICI, although we further demonstrate that this effect extends into the post-LICI (and post-SP) period and corresponds with an increase in net corticomotor excitability. In keeping with previous studies (Chu et al. 2008; McDonnell et al. 2006; Muller-Dahlhaus et al. 2008; Sanger et al. 2001; Werhahn et al. 1999), we interpret the reduction in SICI as a form of disinhibition, probably through activation of presynaptic GABAB receptors. Thus although disinhibition is in effect during LICI, we report here a newly identified post-LICI period during which disinhibition prevails that we refer to as late cortical disinhibition (LCD).

**SICI and the relationship to disinhibition**

SICI provides an index of instantaneous (net) inhibition mediated by fast ionotropic postsynaptic GABA<sub>γ</sub> receptors that produce an inhibitory postsynaptic potential (IPSPA) with a rise time of about 2 ms (Lambert et al. 1996). TMS can be used to estimate the level of SICI by applying a subthreshold conditioning stimulus (CS) to activate low-threshold inhibitory interneurons, followed 2–3 ms later by a suprathreshold test stimulus (TS), which elicits a MEP that is reduced in amplitude, compared with an unconditioned MEP, depending on the prevailing level of inhibition (Ilic et al. 2002; Kujirai et al. 1993). The magnitude of reduction in test MEP amplitude is used as an index of SICI. The choice of 2 ms as the IPI was made to minimize contamination by excitatory I-wave inputs (Peurala et al. 2008). A range of pharmacological studies modulating GABA<sub>γ</sub>-receptor conductance have supported the link between SICI and GABA<sub>γ</sub>ergic inhibition (Di Lazzaro et al. 2000, 2006; Ilic et al. 2002; Ziemann et al. 1996a).

The triple-pulse paradigm used by Sanger et al. (2001) consisted of a suprathreshold priming stimulus (PS) to elicit LICI, followed 100 ms later (i.e., in the presence of LICI) by a double-pulse (CS/TS) combination to measure SICI. They showed the level of SICI is reduced during LICI and offered a number of lines of argument that this is most likely a result of activation of presynaptic GABA<sub>γ</sub> receptors located on inhibitory interneurons that reduce GABA release and thereby reduce the level of SICI. Pharmacological studies have shown that the GABA<sub>γ</sub> agonist baclofen reduces SICI (McDonnell et al. 2006; Werhahn et al. 1999) and reduces GABA<sub>γ</sub>-mediated inhibitory postsynaptic currents in experimental preparations (Sun and Wu 2009). Chu et al. (2008) followed the Sanger protocol by examining SICI at two time points (100 and 150 ms) and found that SICI was reduced at 100 ms but not at 150 ms. This differs from the present findings—the reason for this is not certain, but it is possible that the selection of one time point (150 ms) may not have been optimal to reveal LCD.

**Excitability and LCD**

LCD was associated with a corresponding late period of corticomotor facilitation, which has been suggested but not substantiated by some previous studies. Valls-Sole et al. (1992) studied a number of IPIs between 5 and 400 ms at various intensities and reported LICI between 60 and 150 ms, with an occasional but nonsignificant facilitation occurring beyond 200 ms at stimulus intensities >1.1 × RMT. Wassermann et al. (1996), using a circular coil at 1.1 × RMT, reported a tendency toward facilitation between 150 and 160 ms, although this did not reach significance. Clauss et al. (1992) also used a circular coil at 1.1 × RMT but did not observe any facilitation following LICI. We found the strength of facilitation to be dependent on stimulus intensity and only a weak effect was observed at 1.1 × RMT, with an intensity of around 1.2 to 1.3 × RMT needed to convincingly show facilitation. An increase in PS intensity increased the duration and strength of LICI and delayed the onset and increased the magnitude of facilitation. It also lengthened the duration of the cortical SP, which was correlated with the onset of facilitation. The SP is thought to arise from mechanisms similar to those responsible for LICI, both involving postsynaptic GABA<sub>γ</sub>-mediated inhibition (Hallett 2007; Werhahn et al. 1999). The SP provides a measure of the duration of inhibition and LICI the depth of inhibition. Thus facilitation is associated with higher stimulus intensities and stronger levels of inhibition and the earlier accounts might have shown a clearer effect if higher stimulus intensities had been used.

The period of facilitation coincided with LCD and it is known from experimental studies that GABA<sub>γ</sub> autoreceptor-mediated disinhibition facilitates excitatory postsynaptic potentials (Mott and Lewis 1991; Otis et al. 1993). It therefore seems likely that disinhibition contributes to facilitation, but that this effect is masked by LICI and becomes apparent only once LICI has resolved. As well, a form of post-LICI rebound depolarization could also contribute to facilitation (Connors et al. 1988; Grenier et al. 1998), although rebound is likely to have a lesser role in the measurement of SICI because TS intensity was adjusted across IPIs to compensate for changes in overall excitability.

![FIG. 3. Time course of short-interval intracortical inhibition (SICI) after PS. Mean index of SICI across subjects as a function of IPI after PS. SICI index is expressed as a percentage ratio of conditioned to unconditioned test MEP amplitude (100% corresponds to no SICI effect). Baseline SICI (53%) measured in the absence of PS. SICI was reduced in strength for all IPIs ≤220 ms (*P < 0.05; **P < 0.01).](https://jn.physiology.org/doi/fig/10.1152/jn.00340.2007)
Physiological mechanisms leading to LCD

Cellular studies of inhibitory neurons have demonstrated that a PS reduces the GABA_A-mediated IPSP evoked by a second test stimulus (paired-pulse depression [PPD]). This is mediated through a reduction in GABA release as a consequence of presynaptic GABA_B-receptor activation and corresponds to presynaptic disinhibition. PPD is maximal when the second stimulus is given between 100 and 200 ms after PS (Davies et al. 1990, 1991; Deisz 1999; Deisz et al. 1997; Diamond et al. 1988; Mott and Lewis 1991; Nathan and Lambert 1991; Otis et al. 1993). Further, the time course of presynaptic disinhibition has a faster onset and slower decay time constant than that of postsynaptic inhibition in the neocortex (Deisz 1999) and hippocampus (Otis et al. 1993), suggestive of the different time courses of disinhibition and LICI in the present study.

A number of differences between pre- and postsynaptic GABA_A receptors may explain the observed differences in their time courses. GABA_B receptors are slow acting metabotropic receptors that exert their effects via coupling to ion channels and second messengers, which differ for pre- and postsynaptic receptors (Kaupmann et al. 1998; Luscher et al. 1997). In particular, presynaptic GABA_B receptors predominantly act to reduce Ca^{2+} influx, which is the trigger for vesicle priming and fusion, and this leads to a decrease in neurotransmitter release corresponding to disinhibition. As well, a second-messenger (G protein) mediated reduction in cyclic AMP levels can reduce the stimulatory effect of Ca^{2+} on vesicle recruitment and is a further mechanism limiting GABA release that may have a different time course (Doze et al. 1995; Lei and McBain 2003; Pfrieger et al. 1994; Sakaba and Neher 2003; Scholz and Miller 1991; Otis et al. 1993). Further, the time course of presynaptic disinhibition has a faster onset and slower decay time constant than that of postsynaptic inhibition in the neocortex (Deisz 1999) and hippocampus (Otis et al. 1993), suggestive of the different time courses of disinhibition and LICI in the present study.

Possible physiological effects of LCD

Release of GABA from inhibitory interneurons can set into effect slow GABA_B-mediated IPSPs, whereas through presynaptic regulation can further limit GABA release until these postsynaptic effects have taken their course. Limiting GABA release can reduce exhaustion of the ready releasable pool of GABA, receptor desensitization, and metabolic demand during GABA reuptake and breakdown (see Lei and McBain 2003). Thus disinhibition during postsynaptic inhibition (LICI) appears to have a physiological role.

Why then should there be a prolongation of these presynaptic effects leading to LCD? GABA activates both ionotropic (GABA_A) and metabotropic (GABA_B) transduction mechanisms and the physiological roles for these mechanisms are different. The perisomatic location of GABA_A receptors and their rapid time course means they are well placed to rapidly regulate or gate neuronal firing (Kang et al. 1994; Nicoll 2004) and they probably have a role in maintaining the temporal fidelity of neuronal output (Lamsa et al. 2005). However, GABA_B inhibition follows a longer time course, GABA_B receptors tend to be located dendritically and span multiple layers in neocortex (Kang et al. 1994), and they require associative neuronal firing to generate sufficient GABA pooling for their activation (Poncer et al. 2000; Scanziani 2000). These characteristics imply a role in the cooperative behavior of neuronal assemblies and GABA_B receptors are known to regulate neuronal synchronization, entrainment, and consequently neuronal rhythms (Brown et al. 2007; Mann and Paulsen 2007; Nicoll 2004; Scanziani 2000). Although rhythmic activity could in principle be entrained purely through inhibitory regulation of excitatory networks, the inclusion of disinhibitory mechanisms also under GABA control enhances the regulatory power of this system. Disinhibition following inhibition could be an active process to facilitate activity in those excitatory neurons that had previously been inhibited and play an important role in resynchronizing and maintaining rhythms in selective neuronal populations.

Conclusion and further implications

We conclude that TMS-induced LICI is associated with a period of disinhibition that outlasts LICI. The identification of a late period in which disinhibition dominates in human motor cortex may provide a window to explore the behavior of excitatory networks at a time when inhibitory effects are restrained. Further, disinhibition may have an essential permissive role in some forms of plasticity (Davies et al. 1991) and is required for inducing long-term potentiation in the frequency range of the theta rhythm (Mott and Lewis 1991) and may be relevant to understanding some TMS interventions such as theta-burst stimulation (Thickbroom 2007). The identification and characterization of LCD therefore has implications in the further refinement of neuromodulation techniques by TMS.

Acknowledgments

We thank Prof. Frank Mastaglia, Dr. Barbara Bliem, and Dr. Florian Müller-Dahlhaus for helpful comments.

Grants

This study was supported by Deutscher Akademischer Austauschdienst, Boehringer-Ingeheim Fonds, the Neurotrauma Research Program of Western Australia, and the Neuromuscular Foundation of Western Australia.

References


Claus D, Weis M, Jahnke U, Plewe A, Brunholz C. Corticospinal conduc-
tion studied with magnetic double stimulation in the intact human. J Neurol

Connors BW, Malenka RC, Silva LR. Two inhibitory postsynaptic poten-
tials, and GABA A and GABAB receptor-mediated responses in neocortex

Davies CH, Davies SN, Collingridge GL. Paired-pulse depression of mono-
synaptic GABA-mediated inhibitory postsynaptic responses in rat hip-

Davies CH, Starkey SJ, Pozza MF, Collingridge GL. GABA autoreceptors

Deisz RA. The GABA(B) receptor antagonist CGP 55845A reduces presyn-
aptic GABA(A) actions in neocortical neurons of the rat in vitro. Neuro-

Deisz RA, Billard JM, Ziegglansberger W. Presynaptic and postsynaptic
GABAB receptors of neocortical neurons of the rat in vitro; differences

Diamond DM, Dunwiddie TV, Rose GM. Characteristics of hippocampal
primed burst potentiation in vitro and in the awake rat. J Neurosci 8:

Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P,
Rothwell JC. Direct demonstration of the effect of lorazepam on the

Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M,
Pascual-Leone A, Rosenow F, Rothwell JC, Ziemann U. State of the art:
pharmacologic effects on cortical excitability measures tested by transca-

Perez-Garcia E, Gassmann M, Bettler B, Larkum ME. The GABAB1b
isoform mediates long-lasting inhibition of dendritic Ca2+ spikes in layer 5

Peurala SH, Muller-Dahlhaus JF, Arai N, Ziemann U. Interference of
short-interval intracortical inhibition (SICI) and short-interval intracortical

Pfrieger FW, Gottmann K, Lux HD. Kinetics of GABAB receptor-mediated
inhibition of calcium currents and excitatory synaptic transmission in hip-

Poncer JC, McKinney RA, Gahwiler BH, Thompson SM. Differential
control of GABA release at synapses from distinct interneurons in rat

Lei S, McBain CJ. Transcranial magnetic stimulation: a primer. Handb Exp

Reis J, Swayne OB, Vandermeer Y, Camus M, Dimyan MA, Harris-Love
M, Perez MA, Ragert P, Rothwell JC, Cohen LG. Contribution of transcranial
magnetic stimulation to the understanding of cortical mecha-

Raiteri M. GABA spillover activates postsynaptic GABA(B) receptors to

Scholz KP, Miller RJ. GABAB receptor-mediated inhibition of Ca2+ currents
and synaptic transmission in cultured rat hippocampal neurons. J Physiol

Sun H, Wu SH. The physiological role of pre- and postsynaptic GABAB receptors
in membrane excitability and synaptic transmission of neurons in the rat’s
daoral cortex of the inferior colliculus. Neuroscience 160: 198–211,
2009.

Thickbroom GW. Transcranial magnetic stimulation and synaptic plasticity:
experimental framework and human models. Exp Brain Res 180: 583–593,
2008.

Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor
evoked responses to paired transcranial magnetic stimuli. Electroencepha-

YP, Lujan R, Jacobsen LH, Biermann B, Fritschy JM, Vacher CM,
Muller M, Sansig G, Guetg N, Cryan JF, Kaupmann K, Gassmann M,
Oertner TG, Bettler B. Differential compartmentalization and distinct

Wassermann EM, Samii A, Mercuri B, Ikoma K, Oddo D, Grill SE,
Hallett M. Responses to paired transcranial magnetic stimuli in resting,

Wurhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential
effects on motor cortical inhibition induced by blockade of GABA uptake in

