Effect of Volitional Inhibition on Cortical Inhibitory Mechanisms

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INTRODUCTION

Cerebral cortical activity depends on the balance between excitatory and inhibitory systems. The inhibitory systems of the human motor cortex (MI) can be evaluated noninvasively by transcranial magnetic stimulation (TMS) (Hallett 1995). Using paired-pulse techniques, intracortical influences initiated by the conditioning stimulus (CS) modulate the responses produced by the test stimulus (TS). With a subthreshold CS applied at very short interstimulus intervals (ISIs) of 1–5 ms, there is short intracortical inhibition (SICI), while there is intracortical facilitation (ICF) at intervals between 8 and 30 ms (Kujirai et al. 1993). Long intracortical inhibition (LICI) is observed when a suprathreshold CS is applied 50–200 ms prior to TS (Valls-Sole et al. 1992). Absence of inhibition with direct activation of the corticospinal axons with transcranial electrical stimulation and reduced corticospinal waves suggest that both LICI and SICI occur in the cortex (Inghilleri et al. 1993; Kujirai et al. 1993; Nakamura et al. 1997). LICI and SICI seem to have different mechanisms, mediated by different types of neurons. Pharmacologically, SICI is primarily mediated by GABA_A receptors (Ziemann et al. 1996a), while LICI is subserved by GABA_B receptors (Werhahn et al. 1999). In addition, stronger test pulses reveal more SICI, but less LICI (Sanger et al. 2001). Therefore separate populations of neuronal circuits appear to mediate these inhibitory phenomena (Sanger et al. 2001; Ziemann et al. 1996b).

MI excitability is suppressed during volitional inhibition with NoGo tasks (Hoshiyama et al. 1996, 1997; Leocani et al. 2000) but is enhanced before voluntary movement (Reynolds and Ashby 1999; Leocani et al. 2000). SICI is reduced prior to voluntary movement in the agonist (Reynolds and Ashby 1999), suggesting its role in focusing the subsequent excitatory drive to produce the intended movement (Floeter and Rothwell 1999). In contrast, increased SICI during voluntary suppression of movements was seen in a few individuals (Waldvogel et al. 2000) but was not confirmed in a large series. In this study, we evaluated the effect of volitional inhibition of movement on these inhibitory intracortical mechanisms, using a Go/NoGo task; this information may provide insight into the role of these inhibitory processes in controlling voluntary movement.

METHODS

Subjects

We studied seven healthy, right-handed volunteers (5 men and 2 women, mean age 37 yr, range 20–45 yr). All subjects gave their written informed consents. The experiment was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke.

EMG recordings

Motor evoked potentials (MEPs) of the extensor indicis proprius (EIP) and abductor digiti minimi (ADM) muscles of the dominant right arm were recorded using silver–silver chloride surface electromyography (EMG) electrodes placed over these muscles in a belly-tendon montage (for EIP, the active electrode was placed two finger-breadths proximal to the ulnar styloid joint radial to the ulna and the reference electrode was affixed at the ulnar styloid). EMG amplitude was amplified using a conventional EMG machine (Counterpoint, Danlec Electronics, Skovlunde, Denmark) with band-pass between 10 and 2,000 Hz. The signal was digitized at a frequency of 5 kHz and fed into a laboratory computer for further off-line analysis.

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Magnetic stimulation

TMS was delivered through a 7-cm figure-of-eight coil connected to two Magstim 200 magnetic stimulators via a BiStim module (Magstim, Whitland, Dyfed, UK) placed flat on the scalp over the left motor cortex. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. Thus the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus and therefore optimal for activating the corticospinal pathways transsynaptically (Brasil-Neto et al. 1992; Kaneko et al. 1996). With a slightly suprathreshold stimulus intensity, the stimulating coil was moved over the left hemisphere to determine the optimal position for eliciting MEPs of maximal amplitudes in EIP. The optimal position of the coil was then marked on the scalp with a pen to ensure coil placement throughout the experiment. TMS triggering and data acquisition were controlled using a LabVIEW program (National Instrument, Austin, TX) (Kaelin-Lang and Cohen 2000). Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output and was defined as the minimal stimulus intensity required to produce MEPs of >50 μV in ≥5 of 10 consecutive trials. Similarly, we defined MT_{1mV} as the nearest 1% of the maximum stimulator output and as the minimal stimulus intensity required to produce MEPs of >1 mV in ≥5 of 10 consecutive trials. RMT and MT_{1mV} were measured during rest.

Paired-pulse TMS

SICI and ICF were obtained in the resting EIP and ADM according to a previously described paired-pulse TMS protocol (Kujirai et al. 1993) using a subthreshold CS (0.8 RMT) followed by a suprathreshold TS (MT_{1mV}). Single test pulses and paired stimuli with ISIs of 2 and 15 ms were randomly delivered 5 s apart. Twenty trials were recorded for single test and paired pulses at each ISI. For each ISI, the amplitude ratio of mean conditioned MEP to mean control MEP was calculated. SICI and ICF were defined as the MEP ratios obtained at ISIs of 2 and 15 ms. To adjust CS and TS to achieve similar MEP amplitudes in both control and NoGo conditions, we labeled the strength of TMS pulses, as previously described (Sanger et al. 2001), so that RMT and MT_{1mV} were also determined separately with the subjects performing the NoGo task (NG–RMT and NG–MT_{1mV}, respectively).

LICI was obtained in the resting EIP and ADM according to a previously described paired TMS protocol (Valls-Sole et al. 1992) using a suprathreshold CS (MT_{1mV}) followed by a suprathreshold TS (MT_{1mV}) at ISI of 80 ms. NG–MT_{1mV} was used as CS and TS in the Go/NoGo task. LICI was defined as the average amplitude ratio of conditioned MEP following TS to MEP following CS. Sixty and 30 trials were recorded in the Go/NoGo and control conditions, respectively.

The silent period (SP) was measured in 15 trials at a stimulation intensity of MT_{1mV} in moderately active EIP. TMS was set to elicit stimuli only when the EMG activity of EIP was maintained within 10 to 20% of maximal voluntary contraction at least for 1 s (Kaelin-Lang and Cohen 2000). SP duration was defined as the interval between the magnetic stimulus and the first reoccurrence of rectified voluntary EMG activity, which was automatically calculated by a computerized program as previously described (Sohn et al. 2001).

Experimental design

Volunteers sat comfortably in front of the computer screen, with the right arm supported and were asked to remain completely relaxed unless the Go signal was presented. The computer generated a warning signal (yellow circle), followed by either a Go (green circle) or a NoGo (red circle) signal, at a random interval between 500 and 2,000 ms. The Go and NoGo signals were presented in equal proportion and were randomly intermixed. The warning signals were presented randomly between 5 and 8 s. Volunteers were instructed to make a rapid, phasic extension of their right index finger in response to the Go signal and to remain relaxed in response to the NoGo signal. Each block consisted of 60 trials for SICI and ICF (30 trials each) and 30 trials for LICI.

To become familiar with the experiment, volunteers practiced 30 trials before the experiment. One block of 30 trials was then repeated with EMG recordings, and an average Go reaction time was measured. TMS followed the Go or NoGo signal at different intervals in each volunteer. For SICI and ICF, CS was triggered at the average reaction time after either a Go or a NoGo signal (Fig. 1A). For LICI, we set the average reaction time in the middle of two pulses so that CS and TS were triggered 40 ms earlier and later than the average reaction time, respectively (Fig. 1B). Two blocks of 60 trials and two blocks of 30 trials were performed for SICI and ICF and for LICI, respectively. As a control experiment, 60 and 30 paired stimulations for the two experimental types, respectively, were given during rest without reaction tasks.

Statistical analysis

Data are expressed as means ± SE. Test and conditioned MEPs, SICI, ICF, and LICI were compared between Go/NoGo and control conditions, by using the paired t-test. P < 0.05 was regarded as significant.

RESULTS

Reaction time task

All volunteers performed the Go/NoGo task successfully and reliably so that error rates were <4% in all of them. The erroneous trials were excluded from data analysis. Mean reaction time measured in the first experiment for SICI and ICF was 305 ± 17 ms (range 258–366 ms). It was shortened to 290 ± 19 ms (231–364 ms, P < 0.05), when repeated for the
LICI experiment, but highly correlated to the first reaction time in each volunteer ($R^2 = 0.94, P < 0.0005$). During the experiment, the reaction time of each volunteer also tended to become shorter as the trials were repeated. Off-line analysis revealed, in more than 80% of Go trials in each volunteer, MEPs were elicited after the onset of EMG activity of Go responses, but mostly within 80 ms.

**SICI and ICF during NoGo tasks**

NG–RMT ($50.4 \pm 3.0\%$) and NG–MT$_{1mV}$ ($70.9 \pm 3.1\%$) were slightly higher than RMT ($48.7 \pm 2.7\%$) and MT$_{1mV}$ ($68.9 \pm 3.5\%$), but this difference was not statistically significant. MEP amplitudes of EIP evoked by MT$_{1mV}$ ($1.28 \pm 0.11$ mV) were comparable to those by NG–MT$_{1mV}$ ($1.09 \pm 0.07$ mV) (Fig. 2A), suggesting TS intensity was well adjusted between the NoGo and control conditions. Similarly, those for ADM were also comparable ($2.17 \pm 0.48$ and $2.37 \pm 0.56$ mV, respectively) (Fig. 2B). The intensity of CS using 0.8 RMT and 0.8 NG–RMT was presumably well adjusted.

In EIP, SICI inhibition was significantly enhanced during NoGo tasks ($46.6 \pm 7.9\%$) compared with the control condition ($60.4 \pm 5.6\%; P < 0.05$) (Fig. 3A). Conditioned MEP amplitudes at ISI of 2 ms were also significantly smaller in the NoGo ($0.50 \pm 0.08$ mV) than in the control condition ($0.78 \pm 0.11$ mV; $P < 0.05$) (Fig. 2A). A similar change in SICI was also observed in ADM ($40.7 \pm 6.5\%$ in NoGo and $54.4 \pm 6.3\%$ in control, $P < 0.05$) (Fig. 3B), although differences in conditioned MEP amplitudes were not statistically significant ($0.82 \pm 0.12$ mV in NoGo and $1.18 \pm 0.26$ mV in control; $P = 0.13$) (Fig. 2B). Conditioned MEP amplitudes at ISI of 15 ms as well as ICF were comparable in the two conditions (Figs. 2 and 3).

**LICI during NoGo tasks**

The average duration of the silent period was $165 \pm 11.5$ ms (range 131–223 ms). Thus the ISI of 80 ms was apparently within the range of the silent period at MT$_{1mV}$ in all subjects. Almost complete suppression of test MEPs (LICI < 5%) was observed in five volunteers when conditioning stimuli of MT$_{1mV}$ were applied 80 ms earlier, while the other two volunteers showed LICI around 15%. During NoGo tasks, significant disinhibition was observed in both EIP ($6.0 \pm 2.3\%$ in control and $40.5 \pm 16.4\%$ in NoGo; $P < 0.05$) (Fig. 3A) and ADM ($5.0 \pm 1.9\%$ in control and $49.1 \pm 25.4\%$ in NoGo, $P < 0.05$) (Fig. 3B). Accordingly, average test MEP amplitudes were remarkably increased from $0.05 \pm 0.01$ to $1.41 \pm 0.11$ mV in EIP and from $0.07 \pm 0.02$ to $1.68 \pm 0.28$ mV in ADM, respectively ($P < 0.05$, each) (Fig. 2). The changes in LICI were not correlated with those of SICI ($R^2 = 0.08$).

**SICI, ICF, and LICI during Go tasks**

As expected, test MEP amplitudes were significantly increased during Go trials in both EIP ($2.39 \pm 0.18$ mV) and ADM ($4.18 \pm 0.77$ mV) compared with the control condition ($P < 0.05$, each). Accordingly, conditioned MEPs at ISIs of 2 and 15 ms were also significantly increased (Fig. 2). Thus ICF was unchanged during the Go task in both EIP ($119 \pm 5\%$ in Go and $125 \pm 12\%$ in control) and ADM ($131 \pm 7\%$ in Go and $127 \pm 10\%$ in control), but SICI was significantly increased in both the extensor indicis proprius (EIP) and abductor digiti minimi (ADM). In Go, MEPs of all conditions, except conditioned MEPs at ISI of 2 ms in ADM, were significantly increased.

Go and $125 \pm 12\%$ in control) and ADM ($131 \pm 7\%$ in Go and $127 \pm 10\%$ in control), but SICI was significantly increased in both EIP ($75.3 \pm 4.5\%$; $P < 0.05$), while it was unchanged in ADM ($48.8 \pm 8.0\%$).

Similarly, in paired-pulse TMS for LICI, MEPs of both CS and TS were increased significantly in both EIP ($1.41 \pm 0.11$ and $0.08 \pm 0.04$ mV in control and $3.40 \pm 0.67$ and $1.81 \pm 0.44$ mV in Go) and ADM ($1.80 \pm 0.33$ and $0.06 \pm 0.02$ mV in control and $3.24 \pm 0.51$ and $1.45 \pm 0.41$ mV in Go; $P < 0.05$, each) (Fig. 2). A significant disinhibition in LICI was also observed in both EIP ($59.8 \pm 14.7\%$) and ADM ($57.5 \pm 17.5\%; P < 0.05$, each). In four volunteers, LICI inhibition disappeared during Go.
DISCUSSION

Adjustment of CS and TS intensity in paired-pulse TMS

Both SICI and LICI are influenced by the intensity of CS and TS (Sanger et al. 2001). Increased subthreshold CS intensity from 0.7 RMT reduces inhibition of SICI, but, in LICI, increased suprathreshold CS produces more inhibition if the same TS is applied. In contrast, the amount of inhibition is enhanced in SICI but reduced in LICI when TS is increased with the same CS intensity (Sanger et al. 2001). According to previous studies (Hoshiyama et al. 1996, 1997), MEP amplitudes were reduced during NoGo tasks. Thus we attempted to match MEP sizes between the NoGo and control conditions by adjusting the stimulation intensities. As expected, the stimulation intensities in NoGo were slightly higher than those in the control condition. However, even with higher stimulation intensities, MEPs of TS were slightly smaller in the NoGo than control conditions. These results suggest MEP size would be reduced more if the same stimulation intensities were used, consistent with previous findings (Hoshiyama et al. 1996, 1997; Leocani et al. 2000). According to the previous observation (Sanger et al. 2001), the difference in test MEP sizes between NoGo and control in the present study seems to have no significant impact on SICI and LICI.

Effect of NoGo

During NoGo, SICI inhibition was enhanced. This result supports the assumption volitional inhibition of MI excitability occurs in the cerebral cortex (Waldvogel et al. 2000) and also suggests SICI can be a mechanism underlying MI suppression during volitional inhibition. Suppression of MEP was observed not only in agonists but also in other muscles, including antagonists (Hoshiyama et al. 1996, 1997) and the contralateral homologous muscle (Leocani et al. 2000). In the present study, a change in SICI also occurred in both agonist (EIP) and surrounding muscles (ADM). Previous findings as well as ours suggest volitional inhibition of MI occurs rather nonelectively.

In contrast to SICI, LICI inhibition was significantly reduced during NoGo (Fig. 4). As shown in Figs. 2 and 4, this change was quite dramatic in six of seven subjects; in EIP, four subjects who had nearly no MEPs in the control condition showed 10–40% of LICI, while two with 15% of LICI in the control condition showed almost no inhibition at all (80–120% of LICI). This result suggests LICI is not the mechanism mediating volitional inhibition of MI and supports the view that LICI and SICI have different mechanisms. The opposite direction of changes in LICI and SICI also suggests their
different roles in controlling voluntary movements. LICI is thought to have a mechanism similar to that of the silent period following TMS (Werhahn et al. 1999). The average duration of the silent period in our subjects was much longer than 80 ms, suggesting the reliability of LICI in this study. At the ISI of 80 ms, LICI showed maximum inhibition (Valls-Sole et al. 1992). The lack of change in ICF suggests volitional inhibition does not affect this intracortical facilitatory mechanism.

Volitional inhibition of MI during the NoGo task was observed from 100 to \( \leq 500 \) ms after cue (Hoshiyama et al. 1997; Leocani et al. 2000; Waldvogel et al. 2000). Considering the reaction time of the Go response in the same task, this inhibition appears to occur within a broad range around the NoGo reaction, presuming it is the same as the Go response. Assuming that volitional inhibition is maximum at the onset of the NoGo reaction, we attempted to trigger TMS at the onset of average Go reaction time. With repeated trials during the experiment, however, reaction times were shortened. Thus postexperiment off-line analysis revealed, in more than 80% of trials, TMS was delivered after the onset of Go responses, but mostly within 80 ms after its onset. Timing of TMS in this study presumably fit well within the time window of NoGo-related inhibition.

EIP is a small muscle surrounded by many other extensor muscles. Thus the surface EMG signal might be contaminated with activity from other muscles. However, this fact should not affect the present results because the effect of NoGo on SICI and LICI was nonselective. In this study, we compared the effect of Go/NoGo tasks with the resting state. Therefore the changes in SICI and LICI shown in this study might result also from preparation for reaction-time tasks. It has been shown MI excitability is suppressed during the warning period of a reaction-time task, but this suppression is confined to the prime mover (Hasbroucq et al. 1999; Touge et al. 1998). Since NoGo-related suppression occurs without warning (Leocani et al. 2000) and affects many muscles nonselectively (Hoshiyama et al. 1996, 1997; Leocani et al. 2000), MI changes during a NoGo task should be different from those occurring during a warning period. In this study, the changes in SICI and LICI were similar in both EIP and ADM. In addition, TMS was applied after Go/NoGo cues, not during warning periods. Thus these changes are more likely to be related to the NoGo stimulus rather than to the warning stimulus.

Effect of Go

During Go, SICI inhibition was reduced in agonist (EIP) but not in surrounding muscles (ADM). This result is somewhat compatible with the previous observation showing reduced SICI prior to the voluntary movement selectively in the agonist muscle (Reynolds and Ashby 1999). However, we should mention it is difficult to address any change during Go in this study, because of the difference in MI activity between movement (Go) and resting state (control condition) in addition to an increase in both test and conditioned MEP size during Go. The change in LICI was so marked (no inhibition in 4 subjects), as shown in Figs. 2 and 4, that it might be a real phenomenon, but it cannot be proven definitively in this experiment because of the above-mentioned limitations. The conditioned test MEPs in LICI were dramatically increased in all volunteers.

Possible role of SICI and LICI in voluntary movements

Volitional inhibition of movement is a critical component of the response selection processes that contribute to accurate performance and is an important manifestation of the functional integrity of higher executive mechanisms. This inhibitory process does not simply stop the flow of the movement but rather is an active process that can suppress already prepared activation of MI (Hoshiyama et al. 1997). Enhanced inhibition of SICI in the present study supports this concept. Brain activity that is specific to the NoGo reaction has already been observed in the prefrontal cortex in primates (Sasaki and Gemb a 1986) and humans (Sasaki et al. 1993). Neuroimaging studies have shown selective cortical activation related to volitional inhibition in the prefrontal cortex (Garavan et al. 1999) and supplementary motor cortex (Waldvogel et al. 2000). Bilateral activation of these areas may explain nonselective inhibition occurring during NoGo. The present results suggest an inhibitory influence from these association motor areas is related to mechanisms producing SICI. The change in SICI in NoGo is opposite to the selective reduction in inhibition in agonists before and possibly during voluntary movements (Reynolds and Ashby 1999). Therefore SICI may have a role in providing nonselective suppression of voluntary movement in addition to focusing the subsequent excitatory drive to produce the intended movement (Floeter and Rothwell 1999). This pattern of SICI change might be compatible with the concept of focused disinhibition with tonic background inhibition in voluntary movement (Mink 1996).

In contrast to SICI, LICI appears to be unrelated to the direction of voluntary effort, because it is significantly reduced during both Go and NoGo. Because NoGo is also an active process occurring in the motor system, LICI may have a role in maintaining the resting state. LICI would have to be reduced to allow any type or direction of voluntary effort. Previous observations, including the absence of any change in spinal excitability (Fuhr et al. 1991), the failure to suppress the response to double TES (Inghilleri et al. 1993), and marked reduction in the corticospinal waves evoked by TMS (Chen et al. 1999; Nakamura et al. 1997), all suggest LICI at ISIs of more than 50 ms occurs primarily in the cortex, provided LICI shares the same mechanism as the silent period. However, since the conditioning stimulus is suprathreshold, any change in spinal circuits could affect the following test response. Changes in spinal excitability were observed during the warning period of a reaction-time task (Hasbroucq et al. 1999). Thus it could be possible the apparent difference in the behavior of SICI and LICI is at least partly due to confounding spinal effects. Further study is required to address this matter.

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