Clinical Neurophysiology 119 (2008) 2291–2297

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF)

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See Editorial, pages 2175–2176

ARTICLE INFO

Article history:
Accepted 24 May 2008
Available online 23 August 2008

Keywords:
Short-interval intracortical inhibition
Short-interval intracortical facilitation
Human primary motor cortex
Paired-pulse transcranial magnetic stimulation

ABSTRACT

Objective: Short-interval intracortical inhibition (SICI) is a widely used paired-pulse transcranial magnetic stimulation (TMS) measure to assess inhibition in human motor cortex. However, facilitatory processes may contaminate SICI under certain conditions. Here, we specifically address the contribution of short-interval intracortical facilitation (SICF).
Methods: A SICF interstimulus interval (ISI) curve was obtained in nine healthy subjects according to an established paired-pulse TMS protocol [Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I-wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol (Lond) 1998a;511:181–190]. The individual ISI leading to SICF peak1, trough1, peak2, trough2 and peak3 was selected for the subsequent measurement of SICI intensity curves ($SICI_{peak1}$, $SICI_{trough1}$, $SICI_{peak2}$, $SICI_{trough2}$, $SICI_{peak3}$) using intensity variation of the first stimulus (S1) from 50% to 120% of active motor threshold (AMT) in the first dorsal interosseous muscle.
Results: $SICI_{peak1}$ (mean ISI, 1.54 ms) and $SICI_{trough1}$ (mean ISI, 1.97 ms) showed a sigmoid SICI increase with S1 intensity. $SICI_{trough1}$ reached the strongest SICI and was therefore chosen for comparison with the other SICI curves. $SICI_{peak2}$ (mean ISI, 2.61 ms) was U-shaped with a similar increase at low S1 intensities, but a decrease when S1 intensity exceeded 90% AMT. Correlation analyses suggested that this decrease was caused by SICF. $SICI_{trough2}$ (mean ISI, 3.50 ms) and $SICI_{peak3}$ (mean ISI, 4.26 ms) showed considerably less inhibition than $SICI_{trough1}$ over the whole range of S1 intensities.
Conclusions: Findings show that commonly accepted protocols of testing SICI (ISI of 2–3 ms, S1 intensity ~95% AMT) bear the risk of measuring net inhibition contaminated by SICF.
Significance: SICF may contribute to apparently reduced SICI in patients with neurological or psychiatric disorders.

1. Introduction

Short-interval intracortical inhibition (SICI) is a well established paired-pulse transcranial magnetic stimulation (TMS) measure to explore non-invasively inhibition in human motor cortex mediated by the gamma-aminobutyric acid A (GABAA) receptor (Kujirai et al., 1993; Ziemann et al., 1996b; Ziemann et al., 1996c; Di Lazzaro et al., 1998b, 2000, 2006a; Ilic et al., 2002; Müller-Dahlhaus et al., 2008). It has to be acknowledged that SICI is a relatively complex measure which consists of at least two phases of inhibition that occur at distinct interstimulus intervals (ISI) between the subthreshold first (S1) and suprathreshold second (S2) pulse. It is thought that the first phase of inhibition at very short ISI of ~1 ms is, at least to some extent, accounted for by refractoriness of the neural elements that are responsible for the activation of corticospinal neurons, while a second phase of inhibition at longer intervals (~2.0 to 4.5 ms) is a true synaptic inhibition mediated by the GABAA receptor (Fisher et al., 2002; Hanajima et al., 2003; Roshan et al., 2003).

The magnitude of this second phase of SICI depends critically on the intensities of S1 and S2. Variation of S2 intensity at a given subthreshold intensity of S1 typically leads to a U-shaped variation of SICI magnitude. SICI peaks at S2 intensities that result in motor evoked potential (MEP) amplitudes of ~1 mV (Sanger et al., 2001; Daskalakis et al., 2002; Ilic et al., 2002; Stefan et al., 2002; Müller-Dahlhaus et al., 2008). The low end of this curve is

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1388-2457/$34.00
doi:10.1016/j.clinph.2008.05.031

explained by the observation that only late indirect waves (I-waves) but not the first I-wave (I1-wave) of the TMS induced corticospinal volley are inhibited by S1 (Di Lazzaro et al., 1998b), and that low amplitude MEP is produced predominantly by the early recruited I1-wave (Di Lazzaro et al., 1998a). The high end of the U-shaped curve is interpreted as indicating that high-threshold corticospinal neurons are less susceptible to SICI compared to those that are already recruited in MEP of ~1 mV in amplitude (Müller-Dahlhaus et al., 2008). In addition, high intensities of S2 are capable of exciting the corticospinal neurons directly at their descending axons (Di Lazzaro et al., 1998a), thereby circumventing synaptic inhibition of these neurons. For this reason, in most studies the intensity of S2 was set to elicit control MEP of on average ~1 mV in amplitude.

Typically, variation of S1 intensity at a given suprathreshold S2 intensity also results in a U-shaped SICI curve with maximum SICI occurring at S1 intensities ~90% of the active motor threshold, or ~70% of the resting motor threshold (Kujirai et al., 1993; Ziemann et al., 1996c; Schäfer et al., 1997; Ilic et al., 2002; Kossev et al., 2003; Orth et al., 2003). While the low end of the SICI intensity curve is explained by SICI threshold and increasing recruitment of inhibitory interneurons that contribute to SICI, the mechanisms of the high end of this curve are less clear. It was speculated that the decrease of SICI with S1 intensities above those resulting in maximum SICI indicates recruitment of facilitatory processes that superimpose with inhibition and, therefore, that SICI has to be considered a net inhibition at this range of S1 intensities (Ziemann, 2002). One candidate for such a facilitatory process is short-interval intracortical facilitation (SICF) (Tokimura et al., 1996; Ziemann et al., 1998a; Di Lazzaro et al., 1999; Hanajima et al., 2002; Ilic et al., 2002), but whether it contributes to the high end of the SICI intensity curve has not been formally addressed yet.

Apparent deficiency of SICI was described in a multitude of neurological and neuropsychiatric disorders (for review, (Ziemann, 1999; Curra et al., 2002; Chen et al., 2008)), but recent studies shaded some doubt on as to whether these findings truly indicated abnormal SICI or exaggerated facilitation, or both (Bütefisch et al., 2003; MacKinnon et al., 2005). This puts to question by which protocol SICI is determined most appropriately. Here, we sought to investigate specifically the contribution of SICF to the high end of the SICI intensity curve. We demonstrate that SICF explains the decrease of SICI at high intensities of S1, in particular at discrete ISI that lead to strong SICF. In addition, we demonstrate that SICI is most strongly expressed at the individual ISI that results in the first trough of the SICF interstimulus interval curve. From these data, we develop a recommendation how to determine SICI specifically and appropriately.

2. Materials and methods

2.1. Subjects

Nine subjects (two female) aged 30–43 years (mean ± SEM, 35 ± 1 years) participated in the study. None of the subjects had a history of neurological disease or was on CNS-active drugs at the time of the experiment. All the subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained prior to participation. The experiments conformed to the Declaration of Helsinki and were approved by the ethics committee of the Johann Wolfgang Goethe-University of Frankfurt am Main, Germany.

2.2. Recording and stimulation procedures

Subjects were seated comfortably in a reclining chair. The right forearm was placed in a pronated position on the arm rest. MEP was recorded from the right first dorsal interosseous (FDI) muscle by surface EMG, using Ag–AgCl cup electrodes in a belly tendon montage. The EMG raw signal was amplified and band-pass filtered (20 Hz to 2 kHz; Counterpoint Mk2 electromyograph; Dantec, Skovlunde, Denmark), digitized at an A/D rate of 5 kHz (CED Micro 1401; Cambridge Electronic Design, Cambrigde, UK), and stored in a laboratory computer for online visual display and later offline analysis using customized data collection and conditional averaging software (Spike2® for Windows, version 3.05, CED). Focal TMS was applied over the hand area of the dominant (left) primary motor cortex (M1) through a figure-of-eight coil (diameter of each wing, 70 mm) using two Magstim 200 magnetic stimulators (Magstim Company, Carmarthenshire, Wales, UK) with a monophasic current waveform connected to a BiStim Module (Magstim). The coil was held tangentially to the scalp with the handle pointing backwards and rotated away from the mid-line by up to 45°. This way, the current induced in the brain is directed from lateral-posterior to medial-anterior, and the corticospinal system is being activated predominantly transsynaptically via horizontal cortico-cortical connections (Di Lazzaro et al., 2004).

The optimal coil position for eliciting MEP in the right FDI was determined as the site, where stimulation at a slightly suprathreshold stimulus intensity consistently produced the largest MEP. This site was marked with a pen in order to ensure the consistent placement of the coil throughout the experiment. Resting motor threshold (RMT) was determined to the nearest 1% of maximum stimulator output (MSO) as the lowest stimulus intensity which elicited small MEP (>50 μV peak-to-peak amplitude) in at least five of ten consecutive trials. Active motor threshold (AMT) was determined during a slight isometric FDI contraction (~10% of maximum voluntary contraction, monitored by audio-visual feedback of the EMG signal) and measured to the nearest 1% of MSO as the lowest stimulus intensity which produced an MEP of >100 μV in peak-to-peak amplitude as measured from the average of five consecutive sweeps. Finally, MEP_{1mV} was determined as the stimulus intensity which elicited MEP of, on average, 1 mV in peak-to-peak amplitude in the resting FDI.

2.2.1. Short-interval intracortical facilitation (SICF)

The paired-pulse measurements were started by testing SICF as a function of the ISI between S1 and S2. According to an established protocol, the intensity of S1 was set to MEP_{1mV} when given alone and the intensity of S2 was set to 90% RMT (Ziemann et al., 1998a; Hanajima et al., 2002). Sixteen ISI ranging from 1.5 to 4.5 ms were tested in 0.2 ms steps in each subject. SICF testing consisted of four blocks of 40 trials each. Each block was composed of five conditions presented eight times each in pseudo-random order: control (S1 given alone) and four paired-pulse conditions (S1 followed by S2) at one of four different ISI. SICF was expressed by the conditioned mean MEP at a given ISI as a percentage of the mean control MEP in the same block of trials. From these data, individual SICF-ISI curves were generated.

2.2.2. Short-interval intracortical inhibition (SICI)

Previous studies revealed that three peaks of SICF occur at discrete ISI (peak1: 1.1–1.5 ms, peak2: 2.3–2.9 ms, peak3: 4.1–4.5 ms) and that these are separated by troughs (trough1, trough2) without significant facilitation (Ziemann et al., 1998a). In order to test the possibility of a contribution of SICF to SICI, those five ISI resulting in the three peaks and two troughs were selected from each individual SICF-ISI curve. At those five ISI, SICI was recorded as a function of S1 intensity in five different blocks of trials. The SICI intensity curves will be referred to as $SICI_{peak1}$, $SICI_{trough1}$, $SICI_{peak2}$, $SICI_{trough2}$ and $SICI_{peak3}$. For each curve, eight different S1 intensities ranging from 50% to 120% AMT in 10% steps of AMT were ap-