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Associative plasticity in intracortical inhibitory circuits in human motor cortex

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ABSTRACT

Objective: Paired associative stimulation (PAS) is a transcranial magnetic stimulation technique inducing Hebbian-like synaptic plasticity in the human motor cortex (M1). PAS is produced by repetitive pairing of a peripheral nerve shock and a transcranial magnetic stimulus (TMS). Its effect is assessed by a change in size of a motor evoked response (MEP). MEP size results from excitatory and inhibitory influences exerted on cortical pyramidal cells, but no robust effects on inhibitory networks have been demonstrated so far.
Method: In 38 healthy volunteers, we assessed whether a PAS intervention influences three intracortical inhibitory circuits: short (SICI) and long (LICI) intracortical inhibitions reflecting activity of $GABA_A$ and $GABA_B$ interneurons, respectively, and long afferent inhibition (LAI) reflecting activity of somatosensory inputs.
Results: After PAS, MEP sizes, LICI and LAI levels were significantly changed while changes of SICI were inconsistent. The changes in LICI and LAI lasted 45 min after PAS. Their direction depended on the delay between the arrival time of the afferent volley at the cortex and the TMS-induced cortical activation during the PAS.
Conclusions: PAS influences inhibitory circuits in M1.
Significance: PAS paradigms can demonstrate Hebbian-like plasticity at selected inhibitory networks as well as excitatory networks.

1. Introduction

From animal studies it is known that intracortical inhibitory circuits are involved in cortical plasticity in two different ways. (i) In vitro studies have demonstrated that decrease of local inhibitory activity accompanies and promotes the development of long-term potentiation (LTP) (Stelzer and Shi, 1994; Castro-Alamancos et al., 1995) synaptic remodeling and cortical receptive field expansion (Chowdhury and Rasmusson, 2002). (ii) Enduring changes in synaptic efficacy have been observed not only at excitatory synapses, but also at inhibitory ones (Woodin et al., 2003). In humans there is indirect evidence that a decrease of local $GABA_A$ergic inhibition in the motor cortex enhances dramatically the excitability in the intracortical circuitry during motor practice (Ziemann et al., 2001) while blockade of $GABA_B$ inhibition prevents the development of a cortical plasticity artificially induced by TMS (McDonnell et al., 2007). These results fit with the former aspect of involvement of cortical inhibition in plasticity. In this paper we do not address the role of a decrease of local inhibition in development of plasticity, we focus on the development of plasticity at the level of inhibitory synapses during artificial induction of plasticity. Various transcranial magnetic stimulation (TMS) techniques can be used to induce non-invasively "artificial" cortical plastic changes. Here we used the paired associative stimulation (PAS) technique, which may represent associative LTP- or LTD-like plasticity at a cell population level (Stefan et al., 2000; Wolters et al., 2003). PAS has not been shown so far to be accompanied by lasting changes of short-interval intracortical inhibition (SICI) involving $GABA_A$ receptors or of afferent inhibition (Stefan et al., 2002; Quartarone et al., 2003; Rosenkranz and Rothwell, 2006). Yet according to the prolongation of the silent period (SP, thought to involve $GABA_B$ inhibition) after PAS (Stefan et al., 2000; Quartarone et al., 2003), implication of $GABA_B$ inhibition in PAS-induced after effects has been suggested. This has to be confirmed as SP is a complex parameter involving spinal as well as cortical mechanisms (Fuhr et al., 1991) and evidence for a contribution of $GABA_B$ receptor activation to the SP is weak and controversial (Paulus et al., 2008).

We investigated the aftereffects of a PAS intervention on the excitability of several intracortical inhibitory circuits: those involving $GABA_A$ (SICI) and $GABA_B$ (LICI) synapses and also those fed by peripheral sensory inputs. Sensory stimulation can change motor

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cortex excitability. Inhibition of the MEP by peripheral stimulation has been called "long afferent inhibition" (LAI) when the delay between peripheral and TMS stimulation is from 100 to 1000 ms (Chen et al., 1999b; Abbruzzese et al., 2001; Paulus et al., 2008). Transmitters and pathways involved in LAI are unknown.

2. Methods

2.1. Subjects

Experiments were performed on 38 healthy volunteers (19 men, 19 women) aged 19–67 years (mean ± SEM, 35.5 ± 6.1 years) with no history of either neurological or psychiatric disease and a normal neurological examination. Results of 3 subjects were discarded from analysis because their MEPs were highly variable due to sleepiness. The study included three different experiments, and each experiment included several measures. The number of subjects used in each experiment and the number used for calculating the mean value of each measure are indicated in Fig. 1 and Tables 1 and 2), respectively, as all measures were not obtained in all subjects. The experimental protocol was approved by the NINDS Institutional Review Board, and all subjects gave written informed consent. All subjects were right-handed according to the Oldfield handedness inventory (Oldfield, 1971).

2.2. EMG recording

Surface EMG activity (band-pass 10 Hz–2 kHz) was recorded from the right flexor pollicis brevis (FPB) – the target muscle- and the abductor digiti minimi (ADM) muscle, in bipolar belly-tendon arrangements, using a Nicolet Viking electromyograph (Skovlunde, Denmark). Signals were fed into an IBM compatible personal computer (486 DX) with a data acquisition system built with the Labview graphical programming language (sampling rate 5 kHz) (Kaelin-Lang and Cohen, 2000) for further off-line analysis. During the experiments, EMG activity was continuously monitored with visual and auditory feedback to ensure complete relaxation.

2.3. Transcranial magnetic stimulation

Subjects were seated in a comfortable reclining chair. A figure-of-eight shaped coil (7 cm inner diameter for each half) connected to a Bistim-module and two Magstim 200 magnetic stimulators (The Magstim Company, Dyfed, UK) was positioned on the scalp over the left M1. The hot spot for the right FPB muscle was defined as the lowest threshold site evoking a MEP response in FPB accompanied by a clear thumb flexion movement. The coil was positioned with the handle pointing backwards at an angle of 45° to the midline (Brasil-Neto et al., 1992). The hot spot was marked with a pen on the cap worn by the subject; this served as visual reference against which the coil was positioned and maintained by the experimenter.

2.4. Resting motor threshold (rMT)

The resting motor threshold (rMT) was defined as the minimum TMS intensity (measured by altering the stimulator output intensity in 1% decrements) required to elicit at least five FPB MEPs > 50 μV in 10 consecutive trials (Rossini et al., 1994; Rothwell et al., 1999). TMS stimulus intensities were then expressed as percentage of the right FPB rMT.

2.5. Input–output (I–O) curves

With the coil at the hot spot, 7 responses were recorded and averaged at each of a range of intensities. Intensity of stimulation started at the rMT and was increased by steps of 10% × rMT until the MEP size reached a plateau value. Each I–O curve was characterized by 3 parameters: (i) "slope": the slope of a regression line fitted to the steepest part of I–O curve; (ii) "calculated" resting motor threshold (cMT), the intercept of the regression line with the *x* axis, and (iii) the plateau value (MEP max).

2.6. Long interval intracortical inhibition (LICI)

To evoke LICI a suprathreshold conditioning TMS stimulation (CS90) was delivered 90 ms before a test TMS stimulation (TS)

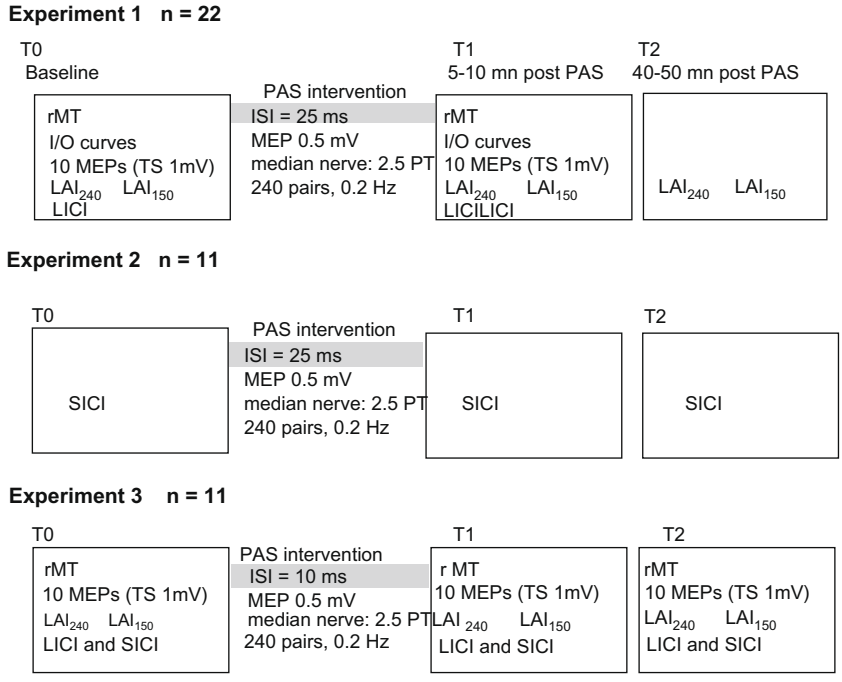

Fig. 1. Experimental designs of the 3 experiments performed.