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Transcranial direct current stimulation modulates the spinal plasticity induced with patterned electrical stimulation

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HIGHLIGHTS

- To study the cortical modulation of spinal plasticity, we examined the effects of giving transcranial direct current stimulation (tDCS) to the motor cortex before PES.
- Applying tDCS before PES modulated the effects of PES on spinal reciprocal inhibition in a polarity specific manner.
- tDCS modulates the tonic pattern of discharge of cortical cells and then affects the descending tonic control exerted by the corticospinal pathways on the spinal interneuron.

ABSTRACT

Objective: Patterned sensory electrical stimulation (PES) has been shown to induce plasticity in spinal reciprocal Ia inhibition of the calf muscles. To study the cortical modulation of spinal plasticity, we examined the effects of giving transcranial direct current stimulation (tDCS) to the motor cortex before PES.
Methods: Seven healthy volunteers participated in this study. PES involved stimulating the left common peroneal nerve at the fibular head with a train of 10 pulses at 100 Hz every 1.5 s for 20 min using an intensity equal to the motor threshold of the tibialis anterior. tDCS was applied for 10 min before PES. For anodal stimulation, the electrode was placed over the motor cortex, and the cathodal electrode over the contralateral supraorbital area. For cathodal stimulation, the electrodes were reversed. Reciprocal inhibition was assessed using a soleus H reflex conditioning-test paradigm.
Results: PES increased disynaptic reciprocal inhibition from the peroneal nerve to the soleus H reflex. When cathodal tDCS was applied before PES, PES no longer increased reciprocal inhibition.
Conclusions: Applying tDCS before PES modulated the effects of PES on spinal reciprocal inhibition in a polarity specific manner.
Significance: We suggest that the motor cortex may play a role in spinal plasticity.

1. Introduction

The brain exerts control over the spinal cord. The short-term impact of cortical activation of the spinal cord has been recognized (Iles and Pisini, 1992; Nielsen et al., 1993). However, the longer lasting effects of the brain on the spinal cord and the mechanisms through which it shapes spinal cord reflex patterns so that they support effective motor control remain poorly understood. Longer lasting plasticity in spinal networks may be important for motor recovery after spinal cord injury (SCI). It is clear that descending activity from the brain gradually changes the spinal cord during development, after supraspinal trauma, and during skill acquisition. Chen et al. (2006a) showed that the corticospinal tract (CST) is essential for acquisition and maintenance of operantly conditioned decrease in the H reflex in rats. They also showed that reciprocal inhibition can be operantly conditioned like the H reflex in rats (Chen et al., 2006b).

Reciprocal inhibition (RI) between agonist and antagonist muscles is mediated by the Ia inhibitory interneurons. Recently, patterned sensory electrical stimulation (PES) was shown to be critical for inducing longer lasting plasticity within the spinally mediated reciprocal Ia inhibitory circuit for the ankle flexor and extensor muscles in human subjects (Perez et al., 2003).

RI conditioning might be used to modify aspects of locomotor and other functional abnormalities associated with spinal cord injuries or other chronic disorders of motor control and might thereby help to produce a more effective function (Chen et al.,

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2005). For example, spinal cord injury in humans is associated with increased stretch reflexes and flexor afferent reflexes and with decreases in RI. These abnormalities are thought to contribute to spasticity (Morita et al., 2001). The conditioning of the RI pathway could be a valuable new method to help achieve more effective spinal cord function in people with incomplete spinal cord injuries or other neurological disorders.

It has been suggested that supraspinal modulation plays an important role in the induction of spinal plasticity. Induction and guidance of activity-dependent spinal plasticity is likely to play an important role in rehabilitation, especially for spinal cord injury.

Few studies, however, have assessed whether supraspinal modulation could affect the changes of spinal reflex in humans (Valero-Cabré et al., 2001; Touge et al., 2001; Perez et al., 2005).

It is known that weak transcranial direct current stimulation (tDCS) induces persisting excitability changes in the cerebral cortex. Anodal stimulation increases and cathodal stimulation decreases cortical excitability (Nitsche and Paulus, 2000). Anodal and cathodal stimulation increase and decrease, respectively, the excitement frequencies of nerve cells (Bindman et al., 1964; Purpura and McMurty, 1965). The aftereffects of tDCS are thought to be related to synapse plasticity due to functions of NMDA receptors in addition to changes in the cell membrane potentials (Nitsche et al., 2003; Liebetanz et al., 2002).

We assessed whether changes in motor cortex excitability induced with tDCS could modulate the aftereffects of PES on the spinal reciprocal Ia inhibitory circuit.

2. Methods

2.1. Participants

Seven healthy adult males (mean age 33.7 ± 8.9 years, all right-handed) participated in this study after providing written informed consent. The investigation was approved by the local ethics committee. None of the subjects had a history of neurological disease or was receiving any acute or chronic medication affecting the central nervous system. The study was performed in accordance with the Declaration of Helsinki.

2.2. Patterned sensory electrical stimulation (PES)

PES consisted of stimulating the common peroneal nerve at the fibular head transcutaneously with a train of 10 pulses (width 1 ms) at 100 Hz every 1.5 s at the intensity of motor threshold for 20 min. The stimulus intensity was set at the motor threshold of the tibialis anterior muscle (TA). The motor threshold of electrical stimulation was defined as the intensity that evoked 100 μV response in TA at resting.

2.3. Transcranial direct current stimulation

The tDCS was applied for 10 min through rectangular saline-soaked sponge electrodes ($50 \times 70\ mm^2$) with a battery-driven stimulator (CX-6650, Rolf Schneider Electronics, Gleichen, Germany). Stimulus intensity was set at 1 mA. One electrode was placed over the primary motor cortex (M1) contralateral to the TA of interest and the other was placed over the ipsilateral supraorbital area. The position of M1 was confirmed through the induction of the largest MEPs in the TA with constant stimulus intensity using transcranial magnetic stimulation (TMS) with a figure-eight stimulation coil connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). Two stimulation conditions (anodal and cathodal) were applied in each subject with a randomized sequence on different days to minimize carry-over effects. Each condition was separated from the preceding one by more than 1 week in the same subject. For anodal stimulation, the anodal electrode was placed over M1, and the cathodal electrode over the supraorbital area. For cathodal stimulation, the electrodes were reversed; that is, the cathodal electrode was placed over M1 and the anodal electrode was placed over the supraorbital area.

2.4. Experiment paradigm (Fig. 1)

Before, immediately after and 10 min after the PES, H reflex and disynaptic RI were examined in all experiments.

The following three conditions were randomly tested in all subjects: paradigm 1, PES only; paradigm 2, anodal tDCS + PES; paradigm 3, cathodal tDCS + PES.

In paradigms 2 and 3, PES followed immediately after the tDCS. To assess direct effects of tDCS on spinal reciprocal inhibition, we assessed RI before, immediately after and 10 min after the cathodal tDCS in five of the seven subjects.

2.5. Reciprocal inhibition (RI)

RI was assessed using a soleus H reflex conditioning-test paradigm. Ten conditioned and 10 test H reflexes were averaged at each time point. The H reflex was elicited by stimulating the tibial nerve at the popliteal fossa (1 ms rectangular pulse). The test soleus H reflex amplitude was maintained at 15–20% of the M max for each block of trials (Crone et al., 1990). Conditioning stimulation to the common peroneal nerve (CPN) was delivered below the fibular head. Stimulus intensity of conditioning stimulation was 1.0× motor threshold (MT). MT was defined as a 100-μV response of the TA. The conditioning-test stimulus interval was set at 0, 1, 2 and 3 ms. The optimal interval for stimulating the CPN to produce disynaptic RI was determined at the beginning of each session and used throughout. The mean values of the test and the conditioned test H reflexes were determined. The amount of RI was defined as: (mean test H reflex amplitude – mean conditioned H reflex amplitude)/mean test H reflex amplitude.

2.6. Analysis

Using two-factor repeated measures ANOVA, we analyzed the effects of stimulation paradigm (PES, anodal tDCS + PES and cathodal tDCS + PES) and time (before, immediately after and 10 min after PES). One factor ANOVA was used to analyze the effects of cathodal tDCS alone on reciprocal inhibition. Post hoc paired *t*-test testing to determine significant comparisons was done using a criterion of $p < 0.05$ with correction for multiple comparisons.

3. Results

At baseline, amounts of RI (mean (SD)), were 18.5% (7.0), 17.7% (9.6) and 14% (3.0) in PES alone, anodal tDCS + PES and cathodal tDCS + PES, respectively. Baseline amounts of RI were not significantly different between stimulation paradigms (ANOVA, $F_{2,28} = 0.80$, $p = 0.46$).

A two-factor repeated measures ANOVA for RI showed a significant interaction of the paradigm (PES, anodal tDCS + PES and cathodal tDCS + PES) and time (before and at interval of stimulation) ($F_{4,24} = 6.22$, $p = 0.001$). In both PES and anodal tDCS + PES groups, the amounts of RI were significantly increased immediately after (post hoc paired *t* test, $p < 0.001$, $p = 0.01$) and 10 min after the stimulation (post hoc paired *t* test, $p = 0.01$, 0.002) compared with the baseline values (Figs. 2a and 2b). The changes in RI were not significantly different between PES and PES + anodal tDCS either immediately after (post hoc paired *t* test, $p = 0.55$) or 10 min after