Peripheral repetitive magnetic stimulation induces intracortical inhibition in healthy subjects

Phillip Krause and Andreas Straube

Department of Neurology, University of Munich, Klinikum Grosshadern, Munich, Germany

Objective: Repetitive magnetic stimulation (rMS) is mainly used in transcranial applications. Only a few works have described its potential peripheral use. The aim of this investigation was to determine if conditioning peripheral (paravertebral) rMS of the cervical nerve roots in a group of healthy subjects induces changes in motor cortical excitability.

Methods: This was measured by means of motor evoked potentials (MEP), motor recruitment curves (RC), intracortical inhibition (ICI) and facilitation, as well as the cortical silent period (CSP) before and after repetitive stimulation. rMS was carried out by applying ten series of stimulation at 120% of resting motor threshold, each lasting 10 seconds with a frequency of 20 Hz. The nerve roots (C7/C8) of the right hand innervating the target muscles (the first dorsal interosseus) were systematically stimulated.

Results: This conditioning rMS caused a significantly longer CSP (p=0.001), increased MEP amplitudes (with a tendency to significance of p=0.06) and raised ICI (p<0.05). These changes were observed on the contralateral side, as well as in the course of RC. In conclusion, previously published results that described a prolonged CSP and increased MEP amplitudes led us to speculate that conditioning peripheral rMS is, like electrical stimulation, capable of influencing motor cortical excitability.

Significance: rMS might therefore be used in rehabilitative strategies for spasticity, pain or central paresis. [Neuro Res 2008; 30: 690-694]

Keywords: Transcranial magnetic stimulation; repetitive magnetic stimulation; motor cortex excitability; motor evoked potentials; intracortical inhibition and facilitation; cortical silent period

INTRODUCTION

Changing the somatosensory input, e.g. by peripheral nerve stimulation, can lead to temporary alterations of the motor cortical excitability of brain areas that correspond to the stimulated body parts. Controversy surrounds the effects induced by such a stimulation. Whereas some works reported no changes in excitability after peripheral stimulation, others found increased motor cortical excitability, which was measured as larger amplitudes of motor evoked potentials (MEP) following the stimulation sessions. A reduction in excitability has also been described.

Nevertheless, several works continue to discuss the potential use of such peripheral stimulation procedures, especially in the rehabilitation of neurological disorders, e.g. after stroke. One limiting factor of electric stimulation devices is the induction of pain before rehabilitatively useful stimulation intensities are reached. As regards the experimental use of such electrical stimulation, it should be mentioned that pain itself may induce changes in cortical excitability.

Repetitive magnetic stimulation (rMS) is another method for stimulating peripheral nerve structures. It is not painful, can also be applied over peripheral nerves or paravertebrally, and has been thought capable of inducing changes in motor cortical excitability. In a previous investigation, we found that the cortical silent period (CSP) in healthy subjects was prolonged following a series of paravertebral rMS. The CSP is a phenomenon of corticospinal inhibition. We hypothesized that such prolongation was induced by the paravertebral rMS on a cortical level. In this study, we therefore measured intracortical inhibition and facilitation of motor cortex areas that correspond to the stimulated side before and after a similar serial stimulation.

METHODS

Subjects

Fifteen healthy subjects without any known neurological disorder took part in the study. Their mean age was 28 years (range: 20-46 years). All gave their informed consent, and the local ethics committee approved the
Peripheral rMS induces intracortical inhibition in healthy subjects: P. Krause and A. Straube

Figure 1: Left: measurement of the CSP, which is defined from the start of the MEP to the return of muscle activity in the pre-contracted muscles. Right: graphic description of the measurement technique of ICI and ICF. With an ISI of 3 ms (ISI3), the MEP response decreases compared to a single stimulus with an ISI of 10 ms (ISI10). It increases.

study. The procedures were in conformance with the Declaration of Helsinki.

Equipment and preparation before measurement
To measure motor cortical excitability, MEP were induced by means of transcranial magnetic stimulation (TMS). Using a single-pulse stimulation paradigm, motor recruitment curves (RC) and the CSP were measured. With a double-pulse paradigm intracortical inhibition (ICI) and facilitation (ICF) were detected.

All experiments were performed using two Magstim 200 stimulators, connected by a Bistim module, and a figure-of-eight magnetic coil (MAGSTIM Company, UK). Each winding of the magnetic coil was 7 cm in diameter. The pulse duration was <1 ms, and the optimal magnetic field was beneath the intersection of the two wings. The coil was placed tangentially to the skull and rotated 45° from the parasagittal plane to induce optimal responses at the location of the ‘motor hot spot’. MEP responses were recorded with surface electrodes affixed to the first interosseous muscle by a two-channel EMG machine.

Before cortical excitability can be measured, the ‘motor hot spot’ of each hemisphere/motor cortex must be determined, using single stimuli of suprathreshold intensities. The location at which the largest MEP response could be detected was marked on the head surface by an Eudermic pen. By reducing the stimulation intensity at this location by 2% stepwise, the resting motor threshold (RMT) was determined for each hemisphere. This was defined as the stimulation intensity, at which five of ten single stimuli led to an MEP response of ~50 μV. The RMT was necessary to define stimulation intensities during the experiment.

Measurements of cortical excitability
After single stimuli were applied to the motor hot spot, the RC and the CSP were measured. To record the RC, stimulation started with an intensity of RMT levels and was increased every ten stimuli by 100–150% of RMT. Therefore, a total of 60 stimuli were given and recorded on each hemisphere.

The CSP was detected by stimulating at 120% of RMT while subjects pre-contracted the recorded muscles (similar paradigm in our earlier study2); Figure 1, left graph).

ICI and ICF were detected with double pulses. A subthreshold (80% of RMT) conditioning (the first) stimulus was followed by a suprathreshold (120% of RMT) test (the second) stimulus with a short interstimulus interval (ISI = 3 ms). This reduces the MEP response, compared to that measured by a single test stimulus (with 120% of RMT) and detects the intracortical inhibitory activity. With a longer ISI (10 ms) the response to the test stimulus increases. This measures intracortical facilitation (Figure 1, right graph).

Conditioning paravertebral rMS
A Magstim Rapid (MAGSTIM Company, UK) for serial magnetic stimulation was used to apply the conditioning stimulation series. A circular coil (diameter: 90 mm) was located paravertebrally over the nerve roots innervating the FDI of the right hand. After the optimal spinal position and the spinal RMT (similar to the cortical RMT) were detected, a total of ten series, each of which lasted 10 seconds, were applied. A frequency of 20 Hz and suprathreshold intensities were used (120% of spinal RMT).

During the stimulation, subjects were instructed to relax both arms. After the serial stimulation, measurements of RC, CSP, ICI and ICF were repeated.

Statistical analysis
Repeated measures ANOVA was used for the statistical analysis separately for RC, ICI, ICF and CSP. The investigated side (left or right hand) and applied stimulation intensity (only during analysis of RC) were submitted as between-subject factors, while time points (before and after cond. rMS) were submitted as within-subject factors. The further post hoc analysis

Neurological Research, 2008, Volume 30, September 691
Peripheral rMS induces intracortical inhibition in healthy subjects: P. Krause and A. Straube

![Graph showing cortical responses](image)

Figure 2: A period of 500 ms during the conditioning stimulation was carried out using Student's t-test for dependent samples.

**RESULTS**

Figure 2 presents a sample of the paravertebral conditioning stimulation. A period of 500 ms for a series of rMS lasting 10 seconds is shown. The responses to each stimulus at ~0.1 mV can be clearly seen.

**Motor recruitment curves**

The RCSs were very similar (Table 1). Separate analysis of the data of each stimulation intensity before and after rMS, as well as for each hemisphere, yielded no statistically significant changes.

Repeated measures ANOVA showed significant differences for the factor stimulation intensity before and after rMS. This is due to the clear increase in MEP responses dependent on the applied stimulation intensity. The comparison of RC (ANOVA) between both sides with corresponding stimulation intensities yielded no statistical differences.

**Duration of the cortical silent period**

ANOVA revealed a significant difference for the time point (before and after cond. rMS) [F(1/10)=18.47; p=0.001]. Furthermore, there was an interaction [F(1/10)=8.6; p=0.01] between time point (before and after cond. rMS) and side of stimulation (left and right).

The duration of CSP increased after the application of rMS on the right hand (left motor cortex). No changes were found for the contralateral side. Figure 4 demonstrates these data graphically. The significant difference for the time points is caused by data for the stimulated (right) side.

![Graph showing normalized data](image)

Figure 4: Normalized data for the ICI and ICF (MEP responses as 100%) are shown. Overall, time differences before and after rMS are clearly visible for the stimulated side; the other side provides very similar data. The increase in ICI (*p<0.05) after rMS on the stimulated side is significant, while the reduction of ICF is not.

ICI=intracortical inhibition; ICF=intracortical facilitation

---

692 Neurological Research, 2008, Volume 30, September
Peripheral rMS induces intracortical inhibition in healthy subjects: P. Krause and A. Straube

Table 1: Data of the motor recruitment curves are presented for both hands before and after rMS. These are averaged with the standard deviation in parentheses. The stimulation intensity is oriented to the motor threshold.

<table>
<thead>
<tr>
<th>Stimulation intensity (%)</th>
<th>Stimulated side (right hand)</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (mV)</td>
<td>After (mV)</td>
</tr>
<tr>
<td>100</td>
<td>0.13 (0.1)</td>
<td>0.08 (0.1)</td>
</tr>
<tr>
<td>110</td>
<td>0.28 (0.1)</td>
<td>0.38 (0.2)</td>
</tr>
<tr>
<td>120</td>
<td>0.79 (0.6)</td>
<td>0.75 (0.4)</td>
</tr>
<tr>
<td>130</td>
<td>1.51 (0.7)</td>
<td>1.66 (0.5)</td>
</tr>
</tbody>
</table>

Motor evoked potentials
The amplitudes of MEP were larger for the right hand after rMS, than for the left; however, they increased on both sides. This trended to be statistically significant for the right hand (p=0.06).

Intracortical inhibition and facilitation
As described before, MEP amplitudes were larger after rMS and more pronounced on the stimulated side. Amplitudes after paired-pulse stimulation for measuring ICI were nearly unchanged before and after rMS. This results in a larger inhibitory activity of the right hand after conditioning rMS. The decrease in the normalized amplitudes in Figure 4 demonstrates this. The analysis (ANOVA) showed this also to be statistically significant (F(1, 20)=5.2; p<0.05).

Furthermore, it should be noted that amplitudes for the ICF paradigm were also smaller after rMS than before. Surprisingly, this was not significant (Table 2).

DISCUSSION
This study not only confirmed previous findings but also revealed new aspects of rMS. For example, a significantly prolonged cortical silent period after the application of rMS at the cervical nerve root level, and a significant increase in the MEP amplitudes after rMS on the stimulated side, but not on the other side. Finally, the increased MEP amplitudes and nearly unchanged amplitudes in the ICI and ICF stimulation paradigm revealed a significant increase in intracortical inhibition.

Although no works have been conducted on peripherally applied rMS and its influences on motor cortical excitability, repetitive magnetic stimulation is widely used to induce transcranial effects that cause changes in cortical excitability. The long-term aim is to develop treatment strategies for different neurological and psychiatric disorders. While rMS applied to peripheral nerve structures is less popular, some works have reported that it can improve motor functions in stroke patients, reduce musculoskeletal pain, and cause a reduction in spasticity.

It has been hypothesized that the cortical effects are induced by peripheral rMS. Our findings support this hypothesis. To our knowledge, no other works have reported such changes in the corticospinal tract after peripheral application of rMS. In our earlier study, the significant prolongation of the cortical silent period led us to speculate that rMS might induce inhibitory effects within the corticospinal tract. Now using the TMS paired-pulse stimulation paradigm, we found an increase in ICI, which was provoked by larger MEP amplitudes to single stimuli and nearly unchanged amplitudes in the ICI paradigm after rMS. The larger MEP amplitudes may point to a higher motor cortical excitability. The increase in ICI might also be a sign of an actively induced process located at the supraspinal level.

Although electric stimulation is different, some works in literature have reported similar changes of increased MEP amplitudes. In only one of these works were ICI and ICF also recorded, but they showed no significant changes after stimulation.

The peripheral application of rMS is another tool allowing changes in the proprioceptive input. Motor cortical excitability, as well as intracortical inhibitory activities, seems to be increased; this might be a sign of an active process. Intracortical facilitation was reduced after rMS, but not significantly; however, this would be appropriate with reduced intracortical inhibition. These results may help, on the other hand, to explain earlier described positive effects of such peripheral rMS, and on the other hand, to open new possibilities for the

Table 2: Data for MEP, ICI, ICF and CSP

<table>
<thead>
<tr>
<th>Stimulated side (right hand)</th>
<th>MEP (mV)</th>
<th>ICI (mV)</th>
<th>ICF (mV)</th>
<th>CSP (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Mean</td>
<td>0.54</td>
<td>0.96*</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.3</td>
<td>0.4</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Adapting (%)</td>
<td>100</td>
<td>100</td>
<td>52.1</td>
<td>34.8**</td>
</tr>
<tr>
<td>Contra lateral side (left hand)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.8</td>
<td>1</td>
<td>0.23</td>
<td>0.32</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Adapting (%)</td>
<td>100</td>
<td>100</td>
<td>48.3</td>
<td>62.2</td>
</tr>
</tbody>
</table>

Values of the ICI and ICF are also adapted to the MEP (expressed in %). The p values are also marked (**p<0.005; ***p=0.001). These markers always refer to the comparison before and after rMS of each paradigm.

Neurological Research, 2008, Volume 30, September 693
Peripheral mRS induces intracortical inhibition in healthy subjects: P. Krause and A. Straube

further development of mRS for neurological rehabilitative strategies.

ACKNOWLEDGEMENT
We wish to thank Ms J. Benson for copyediting the manuscript.

REFERENCES
10. Dishman JD, Ball KA, Burke J. First Prize: Central motor excitability changes after spinal manipulation: A transcranial magnetic stimulation study. J Manipulative Physiol Ther 2002; 25: 2–9
15. Ring H, Rosenthal N. Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilita-
18. Nielson JF, Slinjar T. Long-lasting depression of soleus moto-

694 Neurological Research, 2008, Volume 30, September