The influence of rapid-rate transcranial magnetic stimulation (rTMS) parameters on rTMS effects in Porsolt’s forced swimming test

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Abstract

To assess the similarity of the behavioural effects of the rapid transcranial magnetic stimulation (rTMS) to those produced by other antidepressant treatments, in particular to repeated electroconvulsive shock (ECS), we carried out experiments on Wistar rats. The effects of a standard ECS procedure (9 daily treatments; the current parameters: 150 mA, 50 Hz, 0.5 s) were compared with 18 d treatment with rTMS of the same field intensity of 1.6 T but with different stimulation frequency (20 or 30 Hz) and a different number of sessions (9 or 18). Twenty-four hours after the last treatment the forced swimming test was carried out and the immobility time was recorded. The standard ECT reduced the immobility by 50%, the intensive rTMS (90 or 104 K impulses for the whole period of treatment) caused a significant effect, although smaller than that induced by ECS (reduction by 20–30%). The stimulation at 20 Hz required 18 treatment sessions to produce a significant effect, while only 9 sessions with stimulation at 30 Hz were sufficient to produce a comparable result. This suggests that the effectiveness of rTMS may be augmented by increasing the number or frequency of rTMS impulses.

Key words: Transcranial magnetic stimulation (rTMS), electroconvulsive shock (ECS), forced swimming test, rat.

Introduction

The neurophysiological technique of prolonged repetitive rapid-rate transcranial magnetic stimulation (rTMS) has been proposed as a new physical treatment for depression (Belmaker et al., 1995; George and Wasserman, 1994; Sackeim, 1994; Schlaepfer, 1998; Zyss, 1994). The present clinical results are favourable (Conca et al., 1996; Geller et al., 1997; George et al., 1995, 1997; Pascual-Leone et al., 1996, 1998; Wassermann, 1997). In animal experiments it produced biochemical and behavioural effects regarded as correlating well with clinical activity (Belmaker, 1998; Ben-Shachar et al., 1997; Fleischman et al., 1994, 1995; Fujiki and Steward, 1997; Zyss et al., 1997b).

The rTMS technique is relatively young and therefore no systematic studies on the optimization of its parameters have been carried out in animal experiment (Fleischman et al., 1994; Fujiki and Steward, 1997). Moreover, because of technical problems, the possibilities of using very high frequencies and field intensities are presently limited (Zyss et al., 1997a).

In our previous paper we reported that chronic rTMS similarly to ECS shortened the immobility time in the forced swimming test and produced the decrease in the cAMP response to noradrenaline in cortical slices (Zyss et al., 1997b). The last result, however, did not attain the level of statistical significance.

In the present experiment, using a more powerful apparatus, we investigated whether frequency of the field and intervals between treatments influence the action of repeated rTMS in the forced swimming test, which is regarded as one of the behavioural tests of high predictive value for the action of clinical antidepressants.

Methods and materials

The experiment was carried out on male Wistar rats, 3 months old, weighing 280–330 g, kept in standard animal house conditions, having free access to food and water (room temperature, a 12–12 h light–dark cycle, light on at 06:00 hours). The rats were acclimatized for at least 2 wk before the experiment. All experiments were carried out according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication No.
Table 1. Technical data of our prototype magnetic stimulator MS-3

<table>
<thead>
<tr>
<th>Pulses output</th>
<th>Coil dependent data</th>
<th>Measuring and monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>( U_{\text{out max}} = 1000 ) V</td>
<td>( 2R_{\text{ext}} = 7-14 ) cm</td>
<td>The main computer display</td>
</tr>
<tr>
<td>( I_{\text{out max}} = 5000 ) A</td>
<td>( R = 5-10 ) M( \Omega )</td>
<td>2 voltage displays</td>
</tr>
<tr>
<td>( B_{\text{out max}} = 1.6 ) T</td>
<td>( L = 15-30 ) ( \mu )H</td>
<td>2 temperature displays</td>
</tr>
<tr>
<td>( t_{\text{rise}} = t_{\text{decline}} = 100 ) ( \mu )S</td>
<td>( n = 5-15 )</td>
<td>Air and core coils</td>
</tr>
<tr>
<td>Induced pulse shape: monophasic</td>
<td>Power supply</td>
<td>Accessories</td>
</tr>
<tr>
<td>Current direction selectable: normal and reverse</td>
<td>Selectable: internal, manual, external</td>
<td>Coil holder</td>
</tr>
<tr>
<td>Magnetic gradient: max 30 K( \text{T/s} )</td>
<td>Built-in trigger source</td>
<td>Different stimulation coils</td>
</tr>
<tr>
<td>Capacitance ( C = 12 \times 25 ) ( \mu )F = 275 ( \mu )F</td>
<td>Train duration: selectable</td>
<td>Trigger cables</td>
</tr>
<tr>
<td>Repetition rate: selectable; up to 100 Hz</td>
<td>Power consumption</td>
<td>max: 12 kW</td>
</tr>
</tbody>
</table>

The new prototype magnetic stimulator MS-3, constructed in Zdania Inc. (Academy of Mining and Metallurgy, Cracow), could generate the rapidly alternating magnetic field with strength up to 1–6 T, a frequency of 100 Hz and maximum train duration time over 10 min (dependent on frequency). The rTMS was administered to animals with a special core coil with water-cooling system. The apparatus specifications are given in Table 1.

For magnetic stimulation the rats were placed in special tubes for their immobilization during the session. The core-coil was held immediately above the rat’s head – the centre of the coil above the vertex of the skull; the coil–skin distance did not exceed 1 cm. Maximal output of magnetic stimulator was used for the treatment (1.6 T).

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The animals were receiving magnetic stimulation in sessions varying in both number and magnetic field pulse frequency, spanning 18 d (Table 2). The total number of magnetic impulses received varied between 54 and 108 K \( [K = \text{kilo} (10^3)] \). After completion of the treatment the rats were tested for their behaviour in the forced swimming test.

Table 2. The effect of rTMS of various parameters on the immobility time in the forced swimming test

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Parameters</th>
<th>Number of sessions</th>
<th>Total magnetic impulses per treatment</th>
<th>( n )</th>
<th>Mean ± s.e.m.</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>9</td>
<td>—</td>
<td>24</td>
<td>100.00 ± 3.37</td>
<td>100.00 ± 3.37</td>
</tr>
<tr>
<td>rTMS 20 Hz, 300 s</td>
<td>9</td>
<td>54 K</td>
<td>16</td>
<td>91.99 ± 3.26 (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTMS 20 Hz, 500 s</td>
<td>16</td>
<td>108 K</td>
<td>16</td>
<td>78.18 ± 3.77*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTMS 30 Hz, 533 s</td>
<td>9</td>
<td>90 K</td>
<td>8</td>
<td>70.55 ± 10.59**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECS 50 Hz, 0.5 s</td>
<td>9</td>
<td>—</td>
<td>23</td>
<td>49.47 ± 4.25***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data are expressed in % of control from two separate experiments, in which the relative mean immobility times after ECS were virtually the same (49.47 and 49.52% of control).

Abbreviations: rTMS, repetitive rapid-rate transcranial magnetic stimulation; ECS, electroconvulsive shock; K, kilo \( (10^3) \); \( n \), number of animals for group; ns, non significant.

\* \( p \leq 0.05 \); \** \( p \leq 0.01 \); \*** \( p \leq 0.001 \).
swimming test (Porsolt et al., 1977). On the day following the last stimulation they were placed for 15 min in a cylindrical container (h = 40 cm; 2r = 18 cm) filled with water (25 °C; the level was 15 cm above the bottom) (adaptation trial). On the following day (48 h after the last rTMS) the trial was repeated and the time of immobility during first 5 min of the test was recorded.

The results were compared with those produced by standard ECS procedure, in which the rats received electric current (150 mA, 50 Hz, 0.5 s) through ear-clip electrodes for 10 consecutive days, and were tested at 24 h (adaptation) and 48 h (recording trial) after the last ECS.

Control rats were held identically to rTMS-treated animals; they were immobilized in plastic tubes and exposed to the acoustic artifacts from magnetic stimulator, but no magnetic field was applied.

The results were analysed statistically using one-way ANOVA followed by the Least Significant Difference test.

Results

The rats receiving at least 90 or 108 K magnetic impulses showed a significant, 20–30% reduction in the immobility time in the forced swimming test, while only insignificant effects (10%, 0.1 > p > 0.05) was observed in rats receiving the total of 54 K impulses. ECS, used as a positive control, very significantly reduced the immobility time by 50% (Table 2).

The mild motor tremor caused by direct effects of magnetic fields on muscle was well tolerated. No apparent changes in the general behaviour of the rats undergoing rTMS were observed immediately after the stimulation, or in later periods, particularly when they were handled at the beginning of a new rTMS session. In contrast, the rats undergoing ECS showed characteristic convulsions and postictal behaviour, and they were irritable on the following day.

Discussion

The present data confirm the earlier reports of Fleischman et al. (1995) and Zyss et al. (1997b) that rTMS in experimental rats induces a reduction in the immobility time in the forced swimming test, and thus indicates the possible clinical effectiveness of the treatment in depression. Our results indicate that the magnetic stimulation must reach some level before clear behavioural effects are to be observed. The effect of rTMS seems to be dependent on stimulation frequency and stimulation time (total number of applied magnetic stimuli). Further studies on the importance of these parameters for the effectiveness of rTMS, based on the preliminary data, are warranted.

The establishing of optimal parameters for rTMS requires further studies, as yet it is not known whether these may produce similarly potent effects as the standard ECS. The results suggest that increasing the rTMS frequency may be at least as effective as an increase in the number of sessions. The present findings seem to be inconsistent with some clinical studies (Geller et al., 1997; Padberg et al., 1998) that suggested no differences between the effectiveness of rTMS and single pulse TMS technique (spTMS uses slow frequencies ≤ 1 Hz).

The possibility that two separate ranges of TMS (one > 20 Hz and the other approx. 1 Hz), may be similarly effective should be considered and tested in an animal model.

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References


