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Sex differences in antidepressant-like effect of chronic repetitive transcranial magnetic stimulation in rats

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurophysiological technique. Pre-clinical and clinical studies supported that rTMS might have antidepressant effects. However, whether antidepressant effect of chronic rTMS is gender-dependent is still unknown. In this study, male and female Wistar rats received 10-day rTMS (4 trains of 15 Hz; 200 stimuli/day; 1.0 T) or control condition, and then were subjected to the forced-swim test (FST). We found that female rats consistently showed higher activity levels than males in FST and revealed the significant effects of gender and rTMS as well as the interaction of gender and rTMS. The result suggested the antidepressant-like effects of chronic rTMS on behavioral components in FST are gender-dependent. The gender discrepancy related to rTMS should not be neglected in antidepressant treatment of rTMS.

Keywords: Antidepressant; Forced-swim test; Gender difference; Repetitive transcranial magnetic stimulation

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique, which activates cerebral tissues through strong impulses of magnetic stimulation generated by a conducting coil (Barker et al., 1985). rTMS can affect brain functions, including attention, memory and speech, etc. (Hallett, 2000). So it has been developed into a diagnostic tools in neurology based on the principle of rTMS (Walsh and Cowey, 2000). Moreover, recent reports indicate that rTMS may have a significant therapeutical potential on psychiatric disorders, such as schizophrenia, obsessive–compulsive disorder, and post-traumatic stress disorder (Rollnik et al., 2000; Post and Keck, 2001). Several evidence resulting from both pre-clinical (Fleischmann et al., 1995; Zyss et al., 1997) and clinical studies (Berman et al., 2000; Sackeim, 2000; Fregni and Pascual-Leone, 2005; Fitzgerald et al., 2006) support the notion that rTMS has therapeutical benefit in depression. Moreover, meta-analysis of rTMS treatment of depression shows a significant but modest efficacy of rTMS treatment for depression (Holtzheimer et al., 2001; Loo and Mitchell, 2005); however, the result is not in agreement with other literatures (Martin et al., 2003; Couturier, 2005). Recent animal studies have shed some light on the mechanisms of action of rTMS, and broadened our understanding of how this intervention, like ECS and other antidepressants, affects brain functioning acutely and chronically (Lisanby and Belmaker, 2000). It is possible that rTMS can provide a safe and painless treatment procedure.

There is a growing interest in gender differences of different psychiatric disorders including major depression. Obviously,

Abbreviations: ACTH, adrenocorticotropic hormone; CORT, corticosterone; ECT, electroconvulsive therapy; FST, forced-swim test; HPA, hypothalamic–pituitary–adrenal; HRT, hormone replacement therapy; MAO, monoamine oxidase; rTMS, repetitive transcranial magnetic stimulation; SSRIs, selective serotonin reuptake inhibitors.

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several substantial literatures have revealed the gender differences in depression (Frackiewicz et al., 2000). The higher prevalence of major depression among women than men in the general population has been consistently observed among adults (Weissman and Klerman, 1977; Lynn and Martin, 1997; Cyranowski et al., 2000; Kendler et al., 2001). In general, the prevalence of major depression in women is about twice than in men (Maier et al., 1999; Gater et al., 1998). Previous studies support gender-related differences in pharmacokinetics and pharmacodynamic properties of antidepressant medications (Yonkers et al., 1992). And men and women with chronic depression show different responsivity to and tolerability of various antidepressant classes including SSRIs, norepinephrinergic tetracyclic antidepressant, and tricyclic antidepressants (Martenyi et al., 2001; Kornstein et al., 2000). Therefore, it is essential to investigate the gender difference in response to antidepressant treatments. However, all investigations of antidepressant treatment of rTMS did not involve both male and female subjects. Nevertheless, seldom studies focused on gender difference of the efficacy of rTMS. It is surprised that few clinical reports of rTMS have implication for gender difference in depression and schizophrenia (Walpoth et al., 2003; Huber et al., 2003).

Many animal models of depression have been proposed, but only a few have been adequately validated. The forced-swim test that we proposed to use in the present study is currently one of the most frequently employed behavioral models for emulating the aspect of depression and evaluating antidepressant activity (Lucki, 1997). The model both resembles depressive illness and is selectively sensitive to clinically effective antidepressant treatments. Even though this model does not have strong face or construct validity for depression in humans, its predictive validity is excellent, with it being sensitive to antidepressant treatments (drugs, ECT, and rapid eye movement sleep deprivation) (Porsolt et al., 1977; Zyss et al., 1997; Asakura et al., 1993). The forced-swim test has been successfully employed to demonstrate the antidepressant effects of rTMS in previous studies (Fleischmann et al., 1995; Zyss et al., 1997; Keck et al., 2000a; Tsutsumi et al., 2002).

The major purpose of the current study is to compare the effects of chronic rTMS on forced-swim behavior in male and female rats. We seek to assess the gender difference in response to chronic rTMS on forced-swim test.

2. Materials and methods

2.1. Animals

Naïve 180–200 g rats of the Wistar strain, originally obtained from Medical Laboratory Animal Center, Sichuan University, were 10–12 weeks old. And total rats have 24 males and 24 females. All animal studies were conducted, according to the guideline for the care and use of laboratory animals approved by local government. The rats were housed in controlled temperature (21±1 °C) and light was set on 12-h dark/12-h light cycle referring light off at 07:00 h. Rats were housed in groups, each group covering 6 same gender rats, with food and water *ad libitum*.

2.2. Chronic rTMS treatment

Rats for rTMS treating were chronically treated with rTMS (male rTMS group, $n=12$; female rTMS group, $n=12$) for 10 days. An available stimulator manufactured by Biomedical Engineering Unit, West China Medical Center, Sichuan University, was used for rTMS. The conscious rats received the simulation by a round prototype coil (55 mm diameter, 15 windings). Each rat was daily given 200 stimuli resulting from 4 trains (1.0 T; 200 μs) at a rate of 15 Hz for 10 days. The stimulus waveform was a biphasic cosine pulse. The initial current direction was clockwise. The trains were separated by 1-min intervals to cool the coil. The coil was tangentially placed above the vertex of skull and handled parallel to the line of the vertebral column, inducing mild motor tremor of the head caused by direct effects on muscle. The control rats (male control group, $n=12$; female control group, $n=12$) received the similar stimulations by placing the coil on the low lumbar spine region, but no rTMS on brain.

2.3. Forced-swim test

After 24 h when given the last rTMS, rats were gently placed into a clear Plexiglas cylinders (40 cm height, 30 cm diameter), and water was constantly filled up to 20 cm height at 25±1 °C. The water was changed as each rat was done the test and the cylinder was thoroughly rinsed in order to remove any potential alarm products excreted by rats. During the first test, rats were forced to swim for 15 min, and at 24 h after the first test, rats were subjected to retest in the water for 5 min on the second test (Porsolt et al., 1977). After done, rats were dried with a towel and returned to their home cages. The second test was recorded on videotape (MI-200, Chengdu Taimeng Technology and Market Co., Ltd., China), and later scored by a researcher blinded to the study. Behavior tests were subsequently scored according to the criteria, including latency, climbing, swimming, and immobility. Latency was defined as the period from the beginning to the end time when the rats firstly presented immobility keeping at least

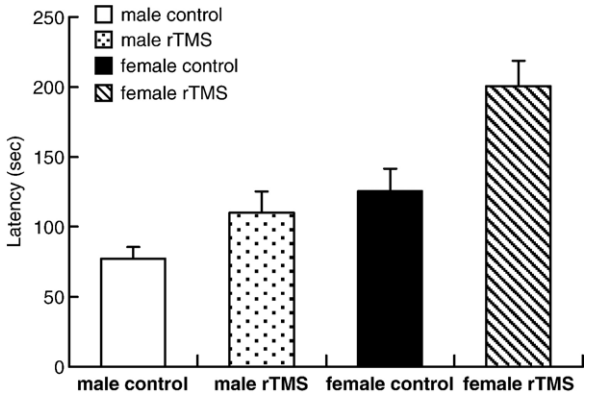

Fig. 1. Effects of rTMS on latency in male and female rats after 10 days of rTMS administration in the forced-swim test. Results demonstrated the significant effects of gender and rTMS, $F_{1,44}=230.478$, $P<0.001$ and $F_{1,44}=138.961$, $P<0.001$, respectively, and the interaction between gender and rTMS, $F_{1,44}=21.327$, $P<0.001$. Data represent mean±S.E.M. ($n=12$ rats per group).