Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 1189–1195

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression

Huirong Zheng [a,1], Li Zhang [a,1], Lingjiang Li [a,d,*], Peng Liu [b], Junling Gao [e], Xiaoyun Liu [b], Juan Zou [a], Yan Zhang [a], Jun Liu [c], Zhijun Zhang [f], Zexuan Li [a], Weiwei Men [g]

[a] Mental Health Institute, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan, China
[b] Department of Radiology, Hunan General Hospital, Changsha, Hunan, China
[c] Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[d] Chinese University of Hong Kong, Hong Kong, China
[e] Division of Neurology, Department of Medicine, University of Hong Kong, Hong Kong, China
[f] The Department of Neuropsychiatry and Institute of Neuropsychiatric Research, affiliated ZhongDa Hospital of Southeast University, Nanjing, China
[g] College of Mathematics, Physics & Information Science, Xinjiang Normal University, Urumqi, China

ARTICLE INFO

Article history:
Received 17 March 2010
Received in revised form 24 May 2010
Accepted 15 June 2010
Available online 23 June 2010

Keywords:
Depression
Magnetic resonance spectroscopy
Myo-inositol
rTMS

ABSTRACT

Background: Neuroimaging studies suggest that the prefrontal cortex (PFC) is involved in the pathophysiology of major depression. Repetitive transcranial magnetic stimulation (rTMS) as an antidepressant intervention has increasingly been investigated in the last two decades. In this study metabolic changes within PFC of severely depressed patients before and after rTMS were evaluated by proton magnetic resonance spectroscopy (1H-MRS).

Method: Thirty-four young depressed patients with treatment-resistant unipolar depression were enrolled in a double-blind, randomized study active ((n = 19) vs. sham(n = 15)), and the PFC was investigated before and after high-frequency (15 Hz) rTMS using 3-tesla proton magnetic resonance spectroscopy. Response was defined as a 50% reduction of the Hamilton depression rating scale. The results were compared with 28 age- and gender-matched healthy controls.

Results: In depressive patients a significant reduction in myo-inositol (m-Ino) was observed pre-rTMS ($p<0.001$). After successful treatment, m-Ino increased significantly in left PFC and the levels no longer differed from those of age-matched controls. In addition to a positive correlation between clinical improvement and an increment in m-Ino ratio, a correlation between clinical improvement and early age onset was observed.

Conclusions: Our results support the notion that major depressive disorder is accompanied by state-dependent metabolic alterations, especially in myo-inositol metabolism, which can be partly reversed by successful rTMS.

1. Introduction

Treatment-resistant depression (TRD) is a common condition with high lifetime personality disorder comorbidity (Souery et al., 2007) and is a risk factor for suicide (Kornstein and Schneider, 2001). Despite its prevalence, the underlying pathophysiology of TRD remains obscure (Berlim and Turecki, 2007). Repetitive transcranial magnetic stimulation (rTMS) techniques have advanced considerably in the last two decades and have been increasingly applied to investigate treatments of TRD (Fitzgerald et al., 2003; Pascual-Leone et al., 1996). High-frequency (5–20 Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC) is usually applied for the treatment of major depression. Meta-analyses suggest rTMS can bring about a significant improvement of depressive symptoms among TRD patients (Gross et al., 2007; Lam et al., 2008; Schutter, 2009). Although the neurobiological mechanisms underlying these effects

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; Cho, choline; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnosis and Statistical Manual of Mental Disorders; Glx, glutamine + glutamate; HAMD, Hamilton Depressive Rating Scale; 1H-MRS, proton magnetic resonance spectroscopy; M-Ino, myo-inositol; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectrum imaging; MT, motor threshold; NAA, N-acetylaspartate; PET, positron emission tomography; PFC, prefrontal cortex; PI, phosphatidylinositol; rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression.

* Corresponding author. Mental Health Institute, The 2nd Xiangya Hospital of Central South University, No. 139 Renmin Zhong Road, Changsha 410011, Hunan, PR China. Fax: +86 731 5360086.
E-mail address: llj2920@163.com (L. Li).

[1] Huirong Zheng and Li Zhang are joint first authors.

0278-5846/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2010.06.009

are unclear (Michael et al., 2003), previous evidences from basic studies have indicated that reduced neurotrophic signaling may be involved in the pathphysiology of depression (Duman 1998). rTMS associated with an induced electric current (Barker et al., 1985) may exert an influence on brain neurotrophic metabolism during neural tuning (Silvanto and Pascual-Leone, 2008; Yukimasa et al., 2006). Moreover, a neurotrophic mode of antidepressant action was also proposed by promoting release of glial cells to increase postsynaptic efficacy (Barres, 2008; Hisaoka et al., 2001).

Glial cells have long been thought to act by providing neurotrophic support for neurons, with little role in information representation or processing. However, increasing evidences indicated that glia have a critical role in neurotransmission, through the uptake and metabolic cycling of phosphoinositide (Auld and Robitaille, 2003). Two-photon imaging study indicated that the astrocytes also play a key role in regulation of neuronal response magnitude and duration (Schummers et al., 2008). The prefrontal cortex (PFC) volume includes DLPFC, anterior cingulate cortex and orbitofrontal cortices; all of these regions have been reported to have glial deficits at postmortem examination and histological studies in patients with major depression (Ongur et al., 1998; Rajkowska, 2000; Rajkowska et al., 1999), suggesting the decrease in myo-inositol (m-Ino). In fact, significant reduction of m-Ino has been reported in the frontal cortex of depressive patients in a postmortem study (Shimon et al., 1997).

However, neurochemical changes are difficult to detect in human brain in vivo. Proton magnetic resonance spectroscopy (^{1}H-MRS) provides an opportunity for noninvasive assessment of cerebral metabolites in clinical research by measurements of N-acetylaspartate (NAA), m-Ino, creatine (Cr), and choline (Cho) (Lyoo and Renshaw, 2002). Some evidence derived from morphological study (Ali et al., 2001), functional imaging studies (Drevets, 2000) and postmortem studies (Ongur et al., 1998; Rajkowska et al., 1999) have shown that the prefrontal region play a critical role in the pathophysiology of depression. In previous positron emission tomography (PET) studies, remission of depressive symptoms was associated with an increased metabolism in the PFC after successful treatment (Bench et al., 1995; Mayberg et al., 2000). It is conceivable that metabolic changes might be accompanied by distinct state-dependent alterations. These alterations would most likely include disturbances of m-Ino metabolism, since it is involved in some aspects of mood disorders (Kim et al., 2005).

M-Ino is a biomarker for glia, and it is actively transported into astrocytes (Barres, 2008). M-Ino is also involved in phospholipid metabolism and plays an important role in a second messenger system involving the phosphatidylinositol (PI) cycle (Belmaker et al., 1990). Thus, m-Ino levels may reflect the functional state of the PI-cycle, which is involved in the pathophysiology and treatment of major depressive disorder (Alvarez et al., 1999; Pandey et al., 2001). Given its widespread presence in glia and utilization within the PFC, alterations in m-Ino are assumed to affect PFC function in mood disorders. Thus, neurotransmitter models of severe mental diseases including dysregulation of m-Ino pathways are widely discussed (Knable et al., 2002).

1H-MRS studies have not consistently demonstrated reduced cortical m-Ino in depression (Frey et al., 1998; Gruber et al., 2003; Kumar et al., 2002), which might be explained by clinical and methodological considerations. Clinical factors, such as the inhomogeneity of patient samples, might obscure changes of m-Ino, if there is no distinction between unipolar versus bipolar subtypes (Davanzo et al., 2003); late versus early onset of disease or familial versus nonfamilial forms (Cecil et al., 2003). Several technical factors in 1H-MRS might also be relevant. First, when spectroscopic imaging data are averaged from multiple cortical regions, this might average out m-Ino reductions due to glial loss with a restricted distribution, such as within the PFC or amygdala (Rajkowska et al., 1999). Second, the proximity of m-Ino to the large water peak in 1H-MRS means that its signal may be affected by unsuppressed water. Additionally, most m-Ino data were acquired at 1.5-T field strength, with limited spectral resolution from Cr, glutamate/glutamine (Glx), and m-Ino signals. These metabolites can be better resolved at higher field strength MRI (Coupland et al., 2005). Therefore, in this study we tested the hypothesis that young adults with resistant unipolar depressions are associated with alterations in m-Ino levels within the PFC as revealed by using 1H-MRS at 3.0 T. Our secondary aim was to identify neurochemical markers of treatment remission after rTMS.

2. Methods and materials

2.1. Subjects

A total of 34 patients fulfilling the diagnostic criteria for major depressive episode (DSM-IV) and referred for rTMS because of drug-treatment resistance were enrolled in this study. The patients were classified as being severely depressed with higher Hamilton Depression Rating Scale (HAMD, ≥24) and length of illness (Table 1). The diagnosis was made independently by two experienced psychiatrists, and all patients' current episode met the DSM-IV depressive episode criteria. Age of the patients was from 18 to 37 years, mean age 27.2 ± 5.2 years, and the mean onset age was 22.0 ± 4.6 years. The patients underwent electroencephalographic and clinical examinations before included into the study. Exclusion criteria were: any other psychiatric axis-I or axis-II disorders, history of epileptic seizures or any other neurological disorder, any kind of metal implants, any other clinically relevant abnormalities in their medical history or laboratory examinations. Patients with a medical history of alcohol or drug abuse were also excluded.

Treatment resistance was defined as failure to respond to at least two different antidepressants given for a period longer than 4 weeks at the maximum recommended dose. All patients were randomly assigned to either the active rTMS group (n = 19) or the sham rTMS group (n = 15). The sample consisted of 22 males and 12 females. There was no significant difference in relevant clinical parameters between patient groups (shown in Table 1). All patients were taking escitalopram 10 mg per day for at least 2 weeks before their enrollment, and they agreed to not change medication during the study. The reason for not discontinuing antidepressant medication was related to the severity of illness and potential suicide risk. After a detailed description of the study to the subjects, written informed consent was obtained. The protocol was approved by the university

Table 1
Clinical and demographic characteristics of responder and non-responder patients with treatment-resistant depression.

Variable	All subjects (n = 34)		Active rTMS (n = 19)		Sham rTMS (n = 15)	
	Mean	SD	Mean	SD	Mean	SD
Age(y)	27.2	5.2	26.9	6.2	26.7	4.3
Gender (male/female)(n)	22/12		12/7		10/5	
marriage(single/married)(n)	19		10/9		9/6	
Onset age(y)	22	4.6	21.7	4.7	21.5	4.2
Course(y)	4.7	3.2	4.8	3.7	4.5	2.7
BDI						
Pre- rTMS	20.2	4.2	21.1	4.2	21	4.2
Post- rTMS	14.9	6.5	13.5*	5.1	19.8	5.1
HAMD						
Pre- rTMS	24.6	2.9	24.6	3	24.6	2.8
Post- rTMS	17.6	6.5	13.5*	5.1	22.9	3.4
Responders	13		12[a]		1	
% improvement	37.8%	19.8	50.1	18.4	23.4	10.1

rTMS, repetitive transcranial magnetic stimulation; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory.
*P < .001, significant difference from pre-rTMS; [a]Fisher's exact test, P < .001.