

Effect of Repetitive Transcranial Magnetic Stimulation on Serum Brain Derived Neurotrophic Factor in Drug Resistant Depressed Patients

R. Zanardini¹, A. Gazzoli², M. Ventriglia³, S. Bignotti², P.M. Rossini³, M. Gennarelli^{1,4}, L. Bocchio-Chiavetto¹

¹ IRCCS "S. Giovanni di Dio", Fatebenefratelli, Brescia, Italy

² Division of Biology and Genetics, Department of Biomedical Sciences and Biotechnologies, University of Brescia, Italy

³ AFaR-Department of Neurosciences, S. Giovanni Calibita-FBF, Isola Tiberina, Rome, Italy

⁴ Neurology, University Campus Biomedico, Rome, Italy

Sommario— Aim of the present investigation was to examine putative effects of rTMS treatment on serum BDNF, a neurotrophic factor with a key role in brain neuroplasticity, in drug resistant depressed patients. Data obtained evidenced an increase in peripheral levels of this neurotrophin after rTMS.

I. INTRODUCTION

There is interesting evidence for the involvement of the neurotrophin brain-derived neurotrophic factor (BDNF) in both the pathophysiology of depression and the mechanism of action of antidepressant treatments. In particular, it has been reported that antidepressant drugs and Electro Convulsive Therapy (ECT) are able to modulate BDNF production and expression. In addition, decreased serum levels of BDNF were found in untreated depressed patients [1] while antidepressant medications appears to normalize this alteration [2].

Several studies reported that repetitive Transcranial Magnetic Stimulation (rTMS) may be useful in treating mood disorders. Although the molecular mechanism by which rTMS elicited this clinical effect is still unclear, preclinical studies reported that rTMS could modulate the hypothalamic-pituitary-adrenocortical (HPA) system and the neurotransmission, inducing modifications in dopamine release and expression of 5-HT_{1A} and N-methyl-D-aspartate receptors. Moreover, rTMS increased BDNF expression in rat brains [3], suggesting that a common molecular mechanism might underlie different pharmacological and non-pharmacological antidepressant strategies.

Aim of the present investigation was to examine the serum levels of BDNF in drug resistant depressed patients before and after rTMS treatment.

II. MATERIALS AND METHODS

After written informed consent 16 patients with major depression diagnosis according to DSM IV criteria (11 females, 5 males; mean age \pm SD 55.94 ± 10.53 years, range 38-69; mean age at onset \pm SD 34.50 ± 9.68 years) and resistant to the pharmacological treatment (stage III definition [4]), were enrolled in the study by the Psychiatric Unit of IRCCS-Fatebenefratelli (Brescia-Italy). Severity of illness had been assessed with the 21 items Hamilton Depression Rating Scale HDRS before (T0) and after (T1) the rTMS treatment. (mean total score \pm SD 18.56 ± 4.44).

TMS treatment consisted of 5 consecutive sessions of stimulation (in the morning) separated by 24 hrs. Frequency of stimulation was 1Hz for 8 subjects and 17 Hz for the remaining 8. Before starting the block of stimulations, and

after the last rTMS treatment clinical evaluation was performed using HDRS scale. At the same time a blood sample was obtained from each subject. BDNF levels were measured by the ELISA method. Statistical evaluations were performed using the SPSS version 11.0 software package (bivariate correlations -Pearson coefficient- and T-tests).

III. RESULTS

rTMS treatment improved significantly depression symptomatology evaluated with HDRS (t-test T0 versus T1: $t=4.702$, $df=15$, $p=0.0003$). No significant difference has been found in BDNF baseline (BDNF₀) levels stratifying patients for gender, age, age at onset and drug treatment. BDNF₀ showed negative correlations with T0 HDRS score ($R=-0.517$, $p=0.04$, Fig. 1).

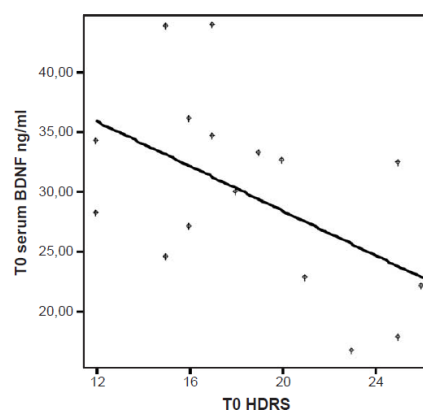


Fig. 1 Correlation between serum levels and HDRS scores in patients before rTMS (T0) ($R=-0.517$, $p=0.040$).

A significant increase of serum BDNF was found after rTMS treatment (BDNF₀ mean value \pm SD: 29.73 ± 8.02 ng/ml, BDNF₁ 32.63 ± 7.59 ng/ml; paired T test: $t=-2.549$, $df=15$, $p=0.022$, Fig. 2). No differences have been observed stratifying patients for high (17R) and low (1R) rTMS frequency.

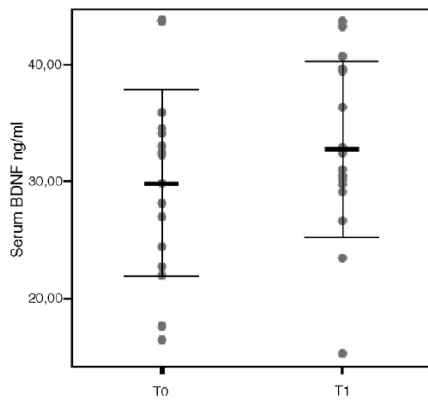


Fig. 2 Serum BDNF levels before (T0) and after treatment with rTMS (T1) ($t=-2.549$, $df=15$, $p=0.022$).

IV. DISCUSSION AND CONCLUSION

Our data show a negative correlation between baseline BDNF concentrations and illness severity. These results extend the relationship between BDNF levels and symptoms severity in drug resistant depression suggesting that BDNF could be a biochemical marker of the illness state.

Moreover, we observe an increase in serum BDNF levels induced by rTMS, suggesting a role of this neurotrophin in antidepressant action of this non pharmacological treatment as firstly evidenced in animal models (Muller et al, 2000). The mechanisms by which rTMS increases peripheral BDNF and whether they reflect a primary condition or a secondary response to neuro-hormonal perturbations remain unclear. The central/peripheral origin and the functional role of blood BDNF has not been clarified yet: beyond brain production, alternative sources can be visceral epithelial cells, endothelial cells, muscle cells, activate macrophages and lymphocytes. However, circulating levels of BDNF might be linked to the brain neurotrophin expression since BDNF can cross the blood-brain barrier through an active transport system and serum levels parallels brain protein expression during neurodevelopment and aging in animal models.

In conclusion our data suggest an involvement of BDNF in the mechanism of action of rTMS treatment, further replications in a larger samples will help to clarify the relevance of this preliminary data.

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