Medical Hypotheses (2008) **71,** 279–282

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Can the 'yin and yang' BDNF hypothesis be used to predict the effects of rTMS treatment in neuropsychiatry?

Andre Russowsky Brunoni [a,b], Paulo Sergio Boggio [c], Felipe Fregni [a,*]

[a] *Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, KS 430, Boston, MA 02215, USA*
[b] *Institute of Psychiatry, University of São Paulo, Brazil*
[c] *Department of Psychology, Mackenzie University, São Paulo, Brazil*

Received 21 February 2008; accepted 29 February 2008

Summary Repetitive transcranial magnetic stimulation (rTMS) is a novel technique of non-invasive brain stimulation which has been used to treat several neuropsychiatric disorders such as major depressive disorder, chronic pain and epilepsy. Recent studies have shown that the therapeutic effects of rTMS are associated with plastic changes in local and distant neural networks. In fact, it has been suggested that rTMS induces long-term potentiation (LTP) and long-term depression (LTD) — like effects. Besides the initial positive clinical results; the effects of rTMS are still mixed. Therefore new tools to assess the effects of plasticity non-invasively might be useful to predict its therapeutic effects and design novel therapeutic approaches using rTMS. In this paper we propose that brain-derived neurotrophic factor (BDNF) might be such a tool. Brain-derived neurotrophic factor is a neurotrophin that plays a key role in neuronal survival and synaptic strength, which has also been studied in several neuropsychiatric disorders. There is robust evidence associating BDNF with the LTP/LTD processes, and indeed it has been proposed that BNDF might index an increase or decrease of brain activity - the 'yin and yang' BDNF hypothesis. In this article, we review the initial studies combining measurements of BDNF in rTMS clinical trials and discuss the results and potential usefulness of this instrument in the field of rTMS.

Introduction

The field of neuromodulation has grown significantly in the past decade. Recent developments and studies in this field have increased our understanding on the physiological effects of neuromodulation; but at the same time, several questions have been raised. One neuromodulatory tool that has been increasingly used is repetitive transcranial magnetic stimulation (rTMS). We propose in this article that brain derived neurotrophic factor (BDNF) might be used to understand and predict the effects of rTMS.

TMS is a novel non-invasive brain stimulation therapy in which a strong magnetic field induces

* Corresponding author. Tel.: +1 617 667 5272.
E-mail address: ffregni@bidmc.harvard.edu (F. Fregni).

0306-9877/$ - see front matter
doi:10.1016/j.mehy.2008.02.011

an electric current in a cortical focal brain area. Because TMS can interrupt brain activity transiently, it was initially used to induce ''virtual brain lesions'', thus exploring the brain-behavior relationship [1]. Later on, it was found that if TMS is applied repeatedly, it can change and modulate focal activity beyond the stimulation period [2]. Therefore, researchers started to explore its neuromodulatory effects in different neuropsychiatric disorders such as major depression, Parkinson's disease, chronic pain, and epilepsy. However, as stated by Ridding and Rothwell [3], rTMS produces a mixture of excitatory and inhibitory effects and it is still unknown how rTMS modifies brain activity and induces long-term, therapeutic effects.

BDNF is a neurotrophin related to neuron survival, synaptic signaling and synaptic consolidation [4]. The main breakthrough in this field was the association of BDNF with brain plasticity; particularly with the phenomenon of long term potentiation and depression (LTP and LTD), which is a property of hippocampus neurons to increase or decrease synaptic strength due to a remote, past stimulus. Here an important difference between mature and precursor BDNF (m- and proBDNF) needs to be underscored. Mature BDNF plays a key role in all stages of LTP, being implicated in early and late LTP; also inducing dendritic and axonal growth and *de novo* gene expression - for a detailed review, see Bramhman and Messaoudi [5]. In contrast, proBDNF, which has affinity to $p75^{NTR}$ death receptors [6], is associated to LTD.

Based on these observations, Lu, Pang and Woo [7] proposed the 'yin and yang' hypothesis for proBDNF and mBDNF; in which mBDNF might be associated with an increase in brain activity and excitability and proBDNF might be associated with an opposite effect: a decrease in brain activity and excitability. Interestingly, both neuropeptides (proBDNF and mBDNF) are in extracellular equilibrium; therefore, for instance, an excessive increase in proBDNF might induce secondarily an increase in mBDNF due to peptide cleavage; thus, resulting in a homeostatic effect.

Therefore, mBDNF expression would be desirable in conditions in which an increase in cortical activity is needed, such as major depression; and proBDNF expression, on the other hand, would be useful in conditions in which an inhibition of cortical excitability is desirable, such as epilepsy.

Similarly, rTMS also induces opposite effects according to the parameters of stimulation. For instance, high frequency (HF) rTMS increases motor cortical excitability and decreases cortical inhibition, and low frequency (LF) rTMS decreases motor cortical excitability [8]. Although, this evidence is supported by electrophysiological measurement methods in healthy subjects; the understanding of the mechanism of action of TMS in other conditions or in other central nervous system (CNS) areas is mainly empirical [3]. In addition, rTMS effects in healthy subjects show a significant variability, such as that up to 20% of subjects receiving LF rTMS have an increase in cortical excitability and similar effects are seen for HF rTMS [9].

Given that rTMS appears to induce LTP and LTD-like effects [3] and BDNF appears to be intimately correlated with these effects [5] we propose to use BDNF as a biological marker to quantify rTMS effects. We further selected three rTMS clinical models to use as a framework to test this 'yin and yang' BDNF hypothesis model.

Clinical models

Major depressive disorder

Based on earlier neuroimaging studies suggesting a left prefrontal lobe dysfunction [10,11]; researchers hypothesized that rTMS would be an ideal tool to revert this dysfunction. Pascual-Leone et al. [12] were the first to demonstrate in a randomized clinical trial that HF rTMS of the left prefrontal cortex is effective to ameliorate major depression. Since then, several clinical studies have been designed — initially with mixed results, probably due to the heterogeneity of stimulation parameters; though more recent studies with different parameters have presented better results [13].

Recent BDNF studies showed that BDNF levels are decreased in MDD subjects [14] and antidepressant treatment leads to an increase in BDNF levels [14]. Similarly, two clinical trials have demonstrated an increase in BDNF levels following rTMS therapy [15,16], whereas one clinical trial demonstrated no significant increase in BDNF levels after rTMS therapy [17]. Nonetheless, these studies were limited by small samples, absence of a control group and previous use of antidepressants in the treatment group. Despite these limitations, these results are in accordance with our hypothesis as HF rTMS that is associated with an increase in cortical excitability increased BDNF levels.

Another interesting, unexplored issue is the potential difference between left and right hemisphere activity in MDD. There are no definite conclusions on this hypothesis, and, in fact, some authors suggested a general prefrontal hypoactivity in MDD [10,18]; however there are studies demonstrating a differential left and right prefrontal activation [19], which seems to be reverted after

treatment [20]. Thus, since excitability-diminishing low frequency rTMS of the right dorsolateral prefrontal cortex also results in a significant improvement of depression, some authors propose that an initial inhibition in this area leads - via transcallosal connections - to an increase in the activity in the left DLPFC (according to the prefrontal hypoactivity hypothesis); whereas other authors suggest that pathological right DLFPC overactivation is an independent feature of depressive disorder [19].

Since BDNF blood levels are lower in depressed patients than in controls and are increased after antidepressant treatment [14], BDNF increases after low-frequency rTMS (that decreases cortical excitability) might be explained by a secondarily increase in left DLPFC activity — via transcallosal connections; therefore the net result of LF rTMS of right DLPFC might be an overall increase in cortical activity, leading to an increase in BDNF levels. In fact, Zanardini et al. [15] observed no differences in BDNF changes when patients were stratified for high- and low-frequency rTMS.

Chronic pain

Chronic pain is a result from a complex mechanism triggered by acute hyperalgesia and followed by profound peripheral and central nervous system (PNS and CNS) changes. In chronic pain, pain is usually not related to peripheral injury or inflammation. In this model, pain induces sensitization in all levels of neuroaxis, but regional differences in plastic changes are often observed. Thus, one must consider that similar stimulation parameters can induce different effects according to the targeted area (e.g., primary motor cortex, sensori-motor cortex, limbic system and spinal cord) and pain origin. For instance, LF rTMS of left and right secondary somatosensory cortex decreased pain in one study, whereas LF rTMS of the primary motor cortex worsened it in another [2]. Indeed these differential plastic changes have also been observed in BDNF animal studies. Duric and McCarson [21] showed that BDNF is down-regulated in hippocampus of rats exposed to pain but up-regulated in the spinal dorsal horn at the same time. Thus, the main question for our model is whether the overall brain activity is significantly increased or decreased, since BDNF blood levels reflect the net BDNF brain changes. Neuroimage and EEG studies in healthy subjects showed that experimental pain induces hyperactivation of several brain areas, including somatosensory areas, insula and superior, middle and inferior frontal cortices [22,23].

Moreover, clinical studies that measured BDNF blood or cerebrospinal fluid levels in chronic pain conditions like fibromyalgia or migraine demonstrated that BDNF levels in these conditions are higher than in healthy controls [24,25]; pointing out that although animal studies have shown BDNF mRNA expression varies along the CNS, BDNF levels in chronic pain are, on average, increased, showing that BDNF levels might index the phenomenon of sensitization. Therefore, in this framework, it might be hypothesized that an effective rTMS treatment for chronic pain is associated with a decrease in BDNF levels. At the same time; the baseline levels of BNDF might be useful to detect patients who would be responders to rTMS treatment if this hypothesis is valid.

Epilepsy

Epileptogenesis is the pathologic transformation of the central nervous system to a state characterized by recurrent unprovoked seizures. Extensive animal and limited human work shows that epileptogenesis involves a potentially reversible increase in excitatory synaptic strength in the region of the seizure focus. In several ways, the changes of epileptogenesis resemble those of LTP. Therefore, LF rTMS could induce a lasting decrease in focal cortical excitability, similarly as LTD. Thus, LF rTMS delivered over a seizure focus may counter (or perhaps reverse) the pathologic hyperexcitability in that area.

As previously stated, mBDNF relates to LTP and proBDNF to LTD. Indeed Koyama and Ikegaya [26] showed that mBDNF is overly expressed in temporal lobe epilepsy, probably due to extensive and continuous hippocampus reorganization. In parallel, it has been shown that excitability diminishing LF rTMS that induces LTD-like phenomenon significantly reduces seizures and decreases epileptiform discharges [27]. Therefore it is conceivable to hypothesize that an effective antiepileptic treatment using rTMS might induce a decrease in BDNF levels. Further studies should explore whether BDNF blood levels can be used to monitor the antiepileptic effect of LF rTMS.

Final thoughts

We have chosen these clinical models because they represent the advances and limitations of both rTMS applications and BDNF findings. Major depression appears to be the prototypical example of BDNF down-regulation, in which rTMS probably acts by inducing its expression. Chronic pain is a complex framework model characterized by plastic changes along the PNS and CNS, in which BDNF can be used to measure the net effects of rTMS on this clinical

condition which appears to be associated with overall increased central nervous system activity. Repetitive TMS for epilepsy is still in its infancy, as BDNF role in epileptogenesis. Nevertheless, mutual research could lead to appealing results.

One major contemporary limitation of BDNF application in rTMS field is that, currently, only BDNF blood levels can be easily assessed, which translate the overall BDNF net effect in the CNS. Mapping BDNF expression along the CNS with noninvasive techniques needs to be further explored.

The combination of repetitive TMS in the clinical field and BDNF assessment seems to be promising. BDNF expression is very dynamic, being up- and down-regulated at the same time along the brain and; hence, BNDF might provide insights not only of the local but also of distant network effects associated with the use of rTMS.

References

[1] Pascual-Leone A, Bartres-Faz D, Keenan JP. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. Philos Trans R Soc London 1999;354:1229—38.

[2] Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract 2007;3:383—93.

[3] Ridding MC, Rothwell JC. Therapeutic use of rTMS. Nat Rev Neurosci 2007.

[4] Allen SJ, Dawbarn D. Clinical relevance of the neurotrophins and their receptors. Clin Sci (Lond) 2006;110:175—91.

[5] Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol 2005;76:99—125.

[6] Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nat Neurosci 2007;10:1089—93.

[7] Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci 2005;6:603—14.

[8] Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 2006;117:2584—96.

[9] Gangitano M, Valero-Cabre A, Tormos JM, Mottaghy FM, Romero JR, Pascual-Leone A. Modulation of input—output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. Clin Neurophysiol 2002;113:1249—57.

[10] Galynker II, Cai J, Ongseng F, Finestone H, Dutta E, Serseni D. Hypofrontality and negative symptoms in major depressive disorder. J Nucl Med 1998;39:608—12.

[11] Brody AL, Barsom MW, Bota RG, Saxena S. Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. Semin Clin Neuropsychiat 2001;6:102—12.

[12] Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233—7.

[13] Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 2007;116:165—73.

[14] Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J Psychiat Res 2007.

[15] Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, et al. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. J Affect Disorders 2006;91:83—6.

[16] Yukimasa T, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda N, et al. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. Pharmacopsychiatry 2006;39:52—9.

[17] Lang UE, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. Psychopharmacology (Berl) 2006.

[18] Steele JD, Currie J, Lawrie SM, Reid I. Prefrontal cortical functional abnormality in major depressive disorder: a stereotactic meta-analysis. Journal Affect Disorders 2007;101:1—11.

[19] Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neurosci 2007;27:8877—84.

[20] Mottaghy FM, Keller CE, Gangitano M, Ly J, Thall M, Parker JA, et al. Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. Psychiat Res 2002;115:1—14.

[21] Duric V, McCarson KE. Neurokinin-1 (NK-1) receptor and brain-derived neurotrophic factor (BDNF) gene expression is differentially modulated in the rat spinal dorsal horn and hippocampus during inflammatory pain. Mol Pain 2007;3:32.

[22] Christmann C, Koeppe C, Braus DF, Ruf M, Flor H. A simultaneous EEG-fMRI study of painful electric stimulation. NeuroImage 2007;34:1428—37.

[23] Maihofner C, Handwerker HO. Differential coding of hyperalgesia in the human brain: a functional MRI study. NeuroImage 2005;28:996—1006.

[24] Laske C, Stransky E, Eschweiler GW, Klein R, Wittorf A, Leyhe T, et al. Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants. J Psychiat Res 2007;41:600—5.

[25] Sarchielli P, Mancini ML, Floridi A, Coppola F, Rossi C, Nardi K, et al. Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome. J Pain 2007;8:737—45.

[26] Koyama R, Ikegaya Y. To BDNF or not to BDNF: that is the epileptic hippocampus. Neuroscientist 2005;11:282—7.

[27] Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. Ann Neurol 2006;60:447—55.