Send Orders for Reprints to reprints@benthamscience.ae

Medicinal Chemistry, **2016**, *12*, **000-000**

The Brain Protective Effect of rTMS (Repetitive Transcranial Magnetic Stimulation) in Depression: A Mini-Review in Animal Studies

Burak Yulug[1,*], Lütfü Hanoglu[1], Ahmet Mithat Tavli[1], Nesrin Helvacı Yılmaz[1] and Ertugrul Kılıc[2]

[1]*Department of Neurology University of Istanbul-Medipol, Istanbul, Turkey;* [2]*Department of Physiology, University of Istanbul-Medipol, Istanbul, Turkey*

Burak Yulug

Abstract: There are rapidly replicating human data suggesting the therapeutic and neurorestorative role of repetitive transcranial magnetic stimulation (rTMS) in clinical depression. However there are only limited experimental studies in the literature and the neurobiological mechanisms of the technique are still unclear. Studies have suggested that modulating of either excitatory or inhibitory neural circuitry may be responsible for the mechanism of action of rTMS while it is still unclear whether rTMS exerts a neuroprotective effect. In the light of these findings, we aimed to review the neuroprotective effect of rTMS in animal models of depression. We have shown that rTMS may exert significant neuroprotective effect through acting on the oxidative injury, stress hormones, dopamine and serotonin levels, Brain Derived Neurotrophic Factor expression, neuroinflamation and hippocampal cell proliferation.

Keywords: Transcranial magnetic stimulation, Neuroprotection, Depression.

1. INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a unique technique giving us the opportunity to stimulate the neurons noninvasively at frequencies between 1 and 50 Hz. Depending on stimulation frequency [1, 2] repetitive TMS can modulate neuronal activity. Low-frequency stimulation induces a transient inhibition, or a decrease in activity, of the cortex [1, 3] while stimulation at high frequencies may activate the cortical neuronal network [1, 4]. The underlying cellular mechanisms behind such inhibition and excitation is unclear. It has been hypothesized that reduced activity in specific synapses [1, 3] or transient increase in the efficacy of excitatory synapses [1, 5] may play an important role in mediating rTMS effects. It has also been postulated that depending on the orientation between the coil and underlying neural tissue it is possible to selectively activate different groups of neuronal networks that may secondary activate or inhibit the cortex [1, 7]. Interestingly, it has been recently shown that stimulation at high frequencies can also induce neuronal plasticity through repeated and regular discharge of synergic cells in a similar manner to the antidepressant effect of serotonin reuptake inhibitors suggesting that rTMS may exert its antidepressant effects partly by potentiating plasticity in the cortex [1, 7, 8]. In contrast to rapidly increasing human data suggesting the neurorestorative effect of rTMS [9], there are only restricted animal studies in the literature [46-66, 68-76]. These studies have demonstrated that rTMS may induce the stimulation of both anti-apoptotic and neuroadaptive pathways that increase the neurotrophic factors and up-regulate the antioxidant, antiexitotoxic and anti-inflammatory activity. One possible explanation for the discrepancy between the human and animal studies could be technical difficulties by delivering the stimulation to the large regions of the brain of a small animal and related large artifacts generated on the recording electrodes that makes the electrophysiological data to focal cortical stimulation in humans irrelevant [10, 11]. This lack of animal data restricts not only our understanding of underlying molecular mechanisms of the neuroprotective effect but also provides a limited animal safety data that prompted us to review the experimental data on Major Depressive Disorder (MDD).

2. THE ROLE OF NEUROINFLAMATION, OXIDATIVE INJURY, AND BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF), IN THE PATHOGENESIS OF DEPRESSION

Major Depressive Disorder (MDD) is a common disorder and a significant cause of disability in the world. This finding was suggested by a very recent research, showing that depression has been found to be the major cause of disability worldwide [12]. It has been recently revealed that MDD worsens the outcome of dementia and also contributes to the death from cardiovascular disease and stroke which are characterized by significant oxidative injury and inflammation [13, 14]. These findings suggest that the underlying pathophysiological feature of depression may be responsible for the worsening of the prognosis of conditions that are also characterized by inflammation. It is well known that depression is associated with chronic, low-grade inflammatory response and related activation of cell-mediated immunity [15]. This hypothesis is supported by various studies demonstrating that stress and depression lead to a reduction of the

*Address correspondence to this author at the Istanbul-Medipol University, Department of Neurology, Istanbul-Turkey; Tel: 0090 506 406 97 14; E-mail: burakyulug@gmail.com

1573-4064/16 $58.00+.00

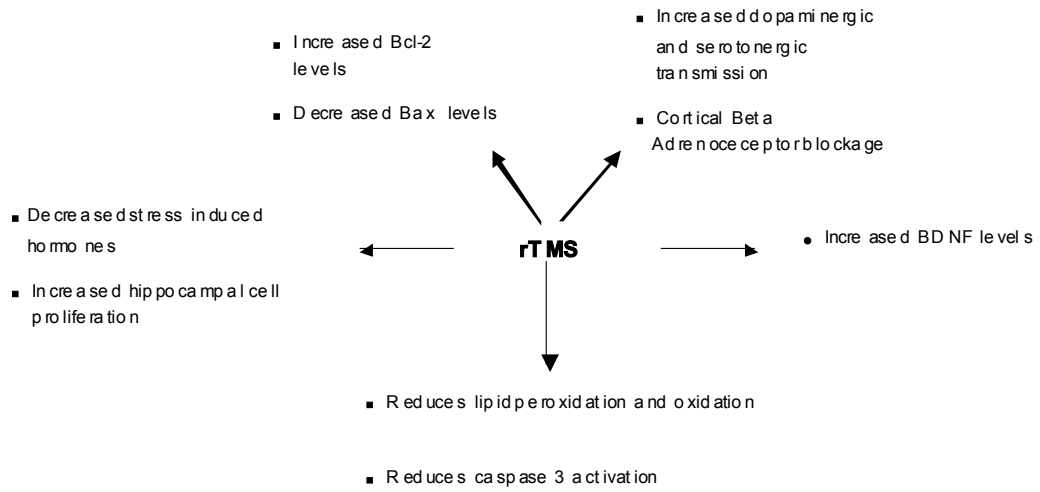

Fig. (1). The underlying mechanisms of the neuroprotective effect of rTMS.

hippocampal volumes which is correlated with a significant neuro-inflammatory response [16-20]. Moreover, in addition to the disturbance of neurotrophic mechanism(s) and impaired levels of glucocorticoid and excitatory neurotransmitters, it has been also shown that the neuroinflammation related oxidative injury may play a significant role by cell death mechanisms of depression [16, 17, 21, 22, 23]. Recent stress-associated, experimental depression studies have shown that depression is associated with an impairment of the total antioxidant defense mechanisms involving increased levels of oxidative injury and altered concentrations of various endogenous antioxidant compounds [24-29] that is in common with the pathogenesis of various neurodegenerative disorders [30, 32]. This finding was suggested by previous studies demonstrating the role of oxidative stress in combination with the pro-inflammatory mechanisms by the development of depression, bipolar disorder, and schizophrenia [30-33]. These findings are in line with a recent study confirming that in experimental olfactory bulbectomy model of depression, the oxidant activity was significantly decreased after the administration of chronic desipramine and lithium treatment [75]. In accordance with this, recent animal studies have demonstrated that chronic mild stress resulted in reduced total antioxidant and peroxidase activity that was reversed by lamotrigine, aripiprazole, and escitalopram administration [34]. Furthermore, human studies revealing that MDD is associated with an increased activity of inflammation, may suggest a common therapeutic role of both antidepressants and anti-inflammatory medications [35, 36]. BDNF is one of the most interesting neurotrophic factors with its antidepressant, anti-inflammatory and neuroprotective effect [20,37-44,76]. Recent studies have shown that central administration of BDNF is associated with the enhancement of the 5HT1A receptor gene expression and also produces antidepressant effect in animal models of depression [37, 77, 78]. This is suggested by Monteggia *et al.* [41] showing that the BDNF knockout mice showed depression-like neurobehavioral deficits that indicated to the role of BDNF in the pathogenesis of depression. However, it has also been shown that BDNF may inhibit neuronal cell death cascades in various brain insults that are mediated through its ability to increase antioxidative enzyme activities and local anti-inflammatory cytokine levels [42-44]. These findings together might open up a new multimodal therapeutic window enabling development of specific pharmacological ligands or exogenously applied techniques to induce potential endogenous antidepressant and neuroprotective pathways in depressive disorder.

3. THE ROLE OF RTMS IN DEPRESSION

There are rapidly replicating evidence showing the degenerative nature of many psychiatric disorders (*i.e.*, depression and schizophrenia) which have lead to an overwhelming progress in basic neuroscience research. However, despite these achievements, treatment opportunities for many psychiatric disorders (*i.e.*, bipolar disorder, depression, and anxiety disorder) are still very limited. Therefore, research focused not only on the development of novel neuropharmacological candidates but also on the complementary strategies that are causally interacting in brain disease pathophysiology and have the potential to enhance neuroprotection in combination with conventional therapeutic approaches. Transcranial magnetic stimulation (TMS) has been shown to be an effective treatment option in the treatment MDD. Recent evidence from meta-analyses suggests that rTMS has a comparable effect with ECT and antidepressant medication in MDD [45]. In the light of these findings, to understand the underlying pathophysiological mechanisms of rTMS in depression, we analyzed and critically reviewed the existing experimental data in animals with depression. Despite limited neuroprotection studies of TMS in animal models of depression, rTMS is an interesting therapeutic option for depression not only with its well defined antidepressant and anxiolytic properties [52-60, 68-73], but also with its effect on the brain regions which are playing a significant role in the pathogenesis of depression.

3.1. The Neuroprotective Role of rTMS in Depression

Keck *et al.* have shown using intracerebral microdialysis that acute rTMS significantly increased the release of dopamine (DA) and its metabolites on the intrahippocampal, in-

traaccumbal and intrastriatal regions in rats which provided the first data that acute rTMS has a modulatory effect on the dopaminergic systems [61]. This suggested that the augmentation in dopaminergic neurotransmission might be associated with the beneficial effects of rTMS in the treatment of major depression. These findings were suggested by two other studies showing that acute repetitive transcranial magnetic stimulation raised the monoaminergic outflow and re-established the dysregulated DA secretion during withdrawal in morphine-sensitized male rats supporting the therapeutic role rTMS in the treatment of drug withdrawal symptoms (i.e sadness and loss of interest symptoms) in humans [62, 63]. Furthermore, a very recent study has shown that subacute administration of rTMS reduced beta-adrenergic receptor binding in cortex, which was in common with electroconvulsive shock (ECS) and other antidepressant treatments that could be interesting in the light of some previous findings showing that the modulation of beta-adrenergic receptors may exert in-vivo neuroprotective effect in focal cerebral ischemia model [64, 65]. Suggesting the neuroprotective effect of rTMS, Müller *et al.* recently evaluated the long-term effects of rTMS on the expression of brain-derived neurotrophic factor (BDNF), in the rat brain [66]. Interestingly, they have revealed that the BDNF mRNA levels were significantly increased after the application of rTMS. These findings were similar with the clinical results of antidepressant drug treatment and electroconvulsive therapy, suggesting the existence of a common molecular mechanism of rTMS and different antidepressant treatment strategies [39,40]. In the light of previous findings showing the neuroprotective effect of BDNF in various experimental models as well as recent studies suggesting the antidepressant effect of BDNF [67], these results together suggest that BDNF may play a significant role by mediating the neuroprotective effects of rTMS. In agreement with this, a very recent study showed that chronic application of rTMS improved the andehonic-like behavior, hippocampal cell proliferation, and BDNF protein level, which lasted even a short period after the discontinuation of rTMS treatment indicating to a strong link between the application of high frequency rTMS and the adaptive neuroplasticity [68].

It is widely known that augmentation in stress hormone levels secondary to the exposure of chronic psychosocial stress may lead to the inhibition of the hippocampal neuronal cell survival [18,68]. In this respect, repetitive transcranial magnetic stimulation might be an interesting neuroprotective candidate for the treatment of depression with its effect on the elevation of stress-induced hormones [69,70] and related neurobehavioral outcomes. Keck et al have recently shown in animals that daily rTMS-treatment of frontal brain regions may strengthen the stress-related coping strategy that was associated with decreased plasma cortisol levels showing parallel therapeutic effects with the antidepressant drugs on the attenuated neuroendocrine response [69]. This was suggested by another animal study of the same group comparing the effect of the repetitive transcranial magnetic stimulation on the anxiety-related swimming behavior in rats. They showed by their interesting study that repetitive transcranial magnetic stimulation improved stress-coping abilities in high-anxiety animals that was associated with decreased elevation of plasma cortisol concentrations secondary to stress [71]. These findings were replicated by Czeh *et al.* showing that simultaneous application of daily psychosocial stress and repetitive transcranial magnetic stimulation treatment normalized the elevation of stress hormones *via* the stabilization of the neuroendocrine axis [70]. In contrast to other studies revealing the beneficial effects of repetitive transcranial magnetic stimulation on the neurogenesis of the hippocampal region [70,73,74], present study demonstrated only a mild effect of rTMS on the reduction of neuronal survival. Moreover, a very recent study by Wang *et al.* using neurobehavioural tests has evaluated the effect of rTMS on the expression of hippocampal pro and anti-apoptotic protein levels as well as the number of bromodeoxyuridine (BrdU)-positive cells after the exposure of chronic stress [72]. They showed interestingly that the chronic stress-induced impairment in behavioral parameters was associated with impaired expression of BDNF and Bcl-2 (B-cell lymphoma protein - 2)/Bax protein levels that was correlated with decreased cell proliferation. However by evaluating the underlying mechanism of the neuroprotective action of rTMS they applied selective CB1 receptor (cannabinoid receptor-1) antagonist that abolished the beneficial effects of rTMS on all neurobehavioural and histological outcomes. This suggested that rTMS may exert its neuroprotective effect *via* the CB1 receptors against chronic unpredictable mild stress (CUMS)-induced changes. This neuroprotective effect was confirmed recently by Tasset *et al.* who demonstrated that rTMS showed a significant effect on oxidative injury by a depression model in rats [75]. Suggesting the oxidative stress hypothesis of depression, they showed that the production of caspase-3 and lipid peroxidation products was reverted towards normality after the treatment of TMS.

4. CONCLUSION

As a conclusion, rTMS is an interesting therapeutic option for MDD not only with its well- known antidepressant effect, but also with the neuroprotective effect that has been shown by various animal models of depression. Further studies evaluating the functional and metabolic correlates of rTMS (*i.e.*, Functional magnetic resonance imaging, FDG-PET) combined with the neurohistological analysis can give us the opportunity to evaluate long-term clinical neuroprotective effects of repetitive transcranial magnetic stimulation in the field of neuropsychiatry research. Moreover, besides their well-known improving effect on clinical symptomatology in depression, these preclinical findings provide strong evidences that might open up a new clinical neuroprotective perspective in neurodegenerative diseases based on neuromodulation.

CONFLİCT OF İNTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us and the con-

tent has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. The authors have no conflicts of interest or any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

REFERENCES

[1] Fitzgerald, Paul, B.; Daskalakis, Z, Jeff. Repititive Magnetic Stimulation Treatment for Depressive Disorders: A Practical Guide, Springer Verlag: Berlin Heidelberg, **2013**, pp. 3-4.

[2] Wassermann, E.M. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. *Electroencephalogr. Clin. Neurophysiol.,* **1998,** *108*(1), 1–16.

[3] Fitzgerald, P.B.; Fountain, S.; Daskalakis, Z.J. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin. Neurophysiol.*, **2006,** *117*(12), 2584–2596.

[4] Chen, R.; Classen, J.; Gerloff, C.; Celnik, P.; Wassermann, E.M.; Hallett, M.; Cohen, L.G. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, **1997,** *48*(5), 1398–1403.

[5] Siebner, H.R.; Peller, M.; Willoch, F.; Minoshima, S.; Boecker, H.; Auer, C.; Drzezga, A.; Conrad, B.; Bartenstein, P. Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. *Neurology*, **2000**, *54*(4), 956–963.

[6] Pascual-Leone, A.; Valls-Sole, J.; Wassermann, E.M.; Hallett, M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain, **1994**, 117, 847–858.

[7] Rothwell, J.C. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J. Neurosci. Methods*, **1997,** 74(2), 113–122.

[8] Branchi, I. The double edged sword of neural plasticity: increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. *Psychoneuroendocrinology*, **2011,** *36*(3), 339–351.

[9] Adeyemo, B.O.; Simis, M.; Macea, D.D.; Fregni, F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. *Front. Psychiatry*, **2012**, *3*,88.

[10] Eric, M.; Wassermann.; Trelawny, Z. Transcranial Magnetic Brain Stimulation: Therapeutic Promises and Scientific Gaps. *Pharmacol. Ther.,* **2012**, *133*, 98–107.

[11] Weissman, J.D.; Epstein, C.M.; Davey, K.R. Magnetic brain stimulation and brain size: relevance to animal studies. *Electroencephalogr. Clin. Neurophysiol.,* **1992**, *85*, 215–219.

[12] Ferrari, A.J.; Charlson, F.J.; Norman, R.E.; Patten, S.B.; Freedman, G.; Murray, C.J.; Vos,T.; Whiteford, H.A. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study. *PLoS Med*., **2013**, *10*(11), e1001547.

[13] Pan, A.; Sun, Q.; Okereke, O.I.; Rexrode, K.M.; Hu, F.B. Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. *JAMA*, **2011**, *306*(11), 1241-1249.

[14] Imran, S.K.; Joseph, J.; Westermeyer, P.G.; Robert, E.F. Depression and Coronary Artery Disease: The Association, Mechanisms, and Therapeutic Implications. *Psychiatry*, **2009,** *6*(1), 38–51.

[15] Michael, B.; Lana, J.W.; Felice, N.J.; Adrienne, O.; Julie ,A.P.; Steven, M.; Nicholas ,B.A.; Amanda, L.S.; Amie, C.H.; Michelle, L.B.; Michael, M. So depression is an inflammatory disease, but where does the inflammation come from*?*. *BMC Med.,* **2013**, *11*, 200.

[16] Lucassen, P.J. What causes the hippocampal volume decrease in depression? *Eur. Arch. Psychiatry Clin. Neurosci.,* **2007**, *257*, 250–260.

[17] Allison, D.J.; Ditor, D.S. The common inflammatory etiology of depression and cognitive impairment: a therapeutic target. *J. Neuroinflammation*, **2014**, *11*, 151.

[18] Heuser, I.; Lammers, C.H. Stress and the brain. *Neurobiol. Aging* , **2003**, S69–S76.

[19] Lu, B.; Gotschalk,W. Modulation of hippocampal synaptic transmission and plasticity by neurotrophins*. Brain Res.,* **2000**, *128*, 231-41.

[20] Frodl, T.; Schüle , C.; Schmitt, G.; Born, C.; Baghai, T.; Zill, P.; Bottlender, R.; Bondy, B.; Reiser, M.; Möller, H.J.; Meisenzahl, E.M. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch. Gen. Psychiatry*, **2007**, *64*, 410–416.

[21] McEwen, B.S. Possible mechanisms for atrophy of the human hippocampus. *Mol. Psychiatry*, **1997**, *2*, 255–262.

[22] Longone, P.; Rupprecht, R.; Manieri, G.A.; Bernardi, G.; Romeo, E.; Pasini, A. The complex roles of neurosteroids in depression and anxiety disorders. *Neurochem*., **2008**, *52*,596–601.

[23] Elenkov, I.J. Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. *Neurochem. Int.* **2008**, *52(1-2*), 40-51.

[24] Rawdin, B.J.; Mellon, S.H.; Dhabhar, F.S.; Epel, E.S,.; Puterman, E.; Su, Y.; Burke H.M.; Reus VI.; Rosser, R.; Hamilton S.P.; Nelson, J.C.; Wolkowitz, O.M. Dysregulated relationship of inflammation and oxidative stress in major depression. *Brain Behav. Immun.,* **2013,** *31*, 143-52.

[25] Siwek, M.; Sowa-Kućma, M.; Dudek, D.; Styczeń, K.; Szewczyk, B.; Kotarska, K.; Misztakk, P.; Pilc, A.; Wolak, M.; Nowak, G. Oxidative stress markers in affective disorders. *Pharmacol Rep*., **2013**, *65*(6), 1558-71.

[26] Cumurcu, B.E.; Ozyurt, H.; Etikan, I.; Demir, S.; Karlidag, R. Total antioxidant capacity and total oxidant status in patients with major depression: impact of antidepressant treatment. *Psychiatry Clin. Neurosci.,* **2009**, *63*, 639–645.

[27] Galecki, P.; Szemraj, J.; Bieñkiewicz, M.; Florkowski, A.; Galecka, E. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. *Pharmacol. Rep.,* **2009**, *61*, 436–447.

[28] Sarandol, A.; Sarandol, E.; Eker, S.S.; Erdinc, S.; Vatansever, E.; Kirli, S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems*. Hum. Psychopharmacol*., **2007**, *22*, 67–73.

[29] Yanik, M.; Erel, O.; Kati, M. The relationship between potency of oxidative stress and severity of depression. *Acta Neuropsychiatrica.,* **2004**, *16*, 200–203.

[30] Berk, M.; Dean, O.Bush. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications*. Int. J. Neuropsychopharmacol.,* **2008**, *11*, 851–876.

[31] Halliwell, B. Free radicals and antioxidants – quo vadis? .*Trends Pharmacol. Sci.,* **2011**, *32*, 125–130.

[32] Halliwell, B. Oxidative stress and neurodegeneration: where are we now?. *J. Neurochem.,* **2006**, *97*, 1634–1658.

[33] Halliwell, B.; Lee C.Y. Using isoprostanes as biomarkers of oxidative stress: some rarely considered issues. *Anti- oxid Redox Signal,* **2010**, *13*, 145–156.

[34] Eren, I.; Naziroğlu,M.; Demirdağ. Protective effects of lamotrigine, aripiprazole and escitalopram on depression-induced oxidative stress in rat brain. *Neuro- chem Res*., **2007**, *32*, 1188–1195.

[35] Nery, F.G.; Monkul, E.S.; Hatch, J.P.; Fonseca, M.; Zunta-Soares, G.B.; Frey, B.N.;
Bowden, C.L.; Soares, J.C. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum. Psychopharmacol*., **2008**, *2*, 87–94.

[36] Muller, N.; Schwarz, M.J.; Dehning, S.; Douhe, A.; Cerovecki, A.; Goldstein-Muller, B.;Spellmann, I.; Hetzel, G.; Maino, K.; Kleindienst, N.; Moller, H.J.; Arolt, V.; Riedel,M. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled,add-on pilot study to reboxetine*. Mol. Psychiatry*, **2006**, *11* (7), 680–684.

[37] Shirayama, Y.; Chen,A.C.; Nakagawa,S.; Russell,D.S.; Duman,R.S. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.,* **2002,** *22*, 3251–3261.

[38] Smith, M.A.; Makino, S.; Kvetnansky, R.; Post, R.M. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J. Neurosci* , **1995**, *15*, 1768–1777.

[39] Nibuya, M.; Morinobu, S.; Duman,R.S. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci*., **1995**, *15*, 7539–7547.

[40] Duman, R.S.; Vaidya, V.A. Molecular and cellular actions of chronic electroconvulsive seizures. *J .ECT.,* **1998**, *14*,181–193.

[41] Monteggia, L.M.; Luikart, B.; Barrot, M.; Theobold, D.; Malkovska,I.; Nef, S.; Parada, L.F.; Nestler, E.J. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol. Psychiatry*, **2007**, *15*, 187–197.

[42] Kim, J.H. Brain-derived neurotrophic factor exerts neuroprotective actions against amyloid β-induced apoptosis in neuroblastoma cells. *Exp. Ther. Med.,* **2014**, *8(*6), 1891-1895.

[43] Jiang, Y.; Wei, N.; Zhu, J.; Lu, T.; Chen, Z.; Xu, G.; Liu, X. Effects of brain-derived neurotrophic factor on local inflammation in experimental stroke of rat. *Mediators Inflamm.,* **2010**, *2010*, 372423.

[44] Bifrare, Y,D.; Kummer, J.; Joss, P.; Täuber, M.G.; Leib, S.L. Brain-derived neurotrophic factor protects against multiple forms of brain injury in bacterial meningitis. *J. Infect. Dis*., **2005**, *191*, 40-45.

[45] Lee, JC.; Blumberger, DM.; Fitzgerald, PB.; Daskalakis, ZJ.; Levinson, AJ. The role of transcranial magnetic stimulation in treatment-resistant depression: a review. *Curr. Pharm. Des.,* **2012**, *18*, 5846-52.

[46] Mongabadi, S.; Firoozabadi, S.M.; Javan, M.; Shojaei, A.; Mirnajafi-Zadeh, J. Effect of different frequencies of repetitive transcranial magnetic stimulation on acquisition of chemical kindled seizures in rats. *Neurol. Sci.,* **2013**, *34*,1897-1903.

[47] Rotenberg, A.; Muller, P.; Birnbaum, D.; Harrington, M.; Riviello, J.J.; Pascual-Leone, A.; Jensen F.E. Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat. *Clin. Neurophysiol*., **2008**, *119*, 2697-702.

[48] Wang, Y.L.; Zhai, Y.; Huo, X.L.; Zhang, J.N. The effect of low frequency transcranial magnetic stimulation on neuropeptide-Y expression and apoptosis of hippocampus neurons in epilepsy rats induced by pilocarpine. *Zhonghua Wai Ke Za Zhi.,* **2007**, *45*, 1685-1687.

[49] Anschel, D.J.; Pascual-Leone, A.; Holmes, G.L. Anti-kindling effect of slow repetitive transcranial magnetic stimulation in rats. *Neurosci. Lett.,* **2003**, *351*,9-12.

[50] Akamatsu, N.; Fueta, Y.;Endo, Y.; Matsunaga, K.; Uozumi, T.; Tsuji, S. Decreased susceptibility to pentylenetetrazol-induced seizures after low-frequency transcranial magnetic stimulation in rats. *Neurosci Lett*., **2001**, *310*,153-156.

[51] Fleischmann, A.; Hirschmann, S.; Dolberg, O.T.; Dannon, P.N.; Grunhaus, L. Chronic treatment with repetitive transcranial magnetic stimulation inhibits seizure induction by electroconvulsive shock in rats. *Biol. Psychiatry*, **1999**, *45*,759-763.

[52] Kanno M.; Matsumoto, M.; Togashi, H.; Yoshioka, M.; Mano, Y. Effects of repetitive transcranial magnetic stimulation on behavioral and neurochemical changes in rats during an elevated plus-maze test. *J. Neurol. Sci.,* **2003**, *211*, 5-14.

[53] Schutter, D.J. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol. Med*., **2009**, *39*(1), 65–75.

[54] Zwanzger, P.; Fallgatter, A.J.; Zavorotnyy, M.; Padberg, F. Anxiolytic effects of transcranial magnetic stimulation-an alternative treatment option in anxiety disorders? *J. Neural. Transm.*, **2009**, *116*, 767-775.

[55] Paes, F.; Machado, S.; Arias-Carrión, O.; Velasques, B.; Teixeira, S.; Budde, H.; Cagy, M.; Piedade, R.; Ribeiro, P.; Huston, J.P.; Sack, A.T.; Nardi, A.E. The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review. *CNS Neurol. Disord. Drug Targets*, **2011**, *10*, 610-620.

[56] Kanno, M.; Matsumoto, M.; Togashi, H.; Yoshioka, M.; Mano, Y. Effects of acute repetitive transcranial magnetic stimulation on extracellular serotonin concentration in the rat prefrontal cortex. *J. Pharmacol. Sci.*, **2013**, *93*, 451-457.

[57] Belmaker, R.H.; Grisaru, N. Magnetic stimulation of the brain in animal depression models responsive to ECS. *J. ECT.,* **1998**, *14*, 194-205.

[58] Slotema, C.W.; Blom, J.D.; Hoek, H.W.; Sommer, I.E. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS) ? a meta- analysis of the efficacy of rTMS in psychiatric disorders. *J. Clin. Psychiatry,* **2010**, *71*(7), 873–884.

[59] Sachdev, P.S.; McBride, R.; Loo, C.; Mitchell, P.M.; Malhi, G.S.; Croker, V.
Effects of different frequencies of transcranial magnetic stimulation (TMS) on the forced swim test model of depression in rats. *Biol. Psychiatry*, **2002**, *51,* 474-479.

[60] Levkovitz, Y.; Grisaru, N.; Segal, M. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. *Neuropsychopharmacology*, **2001**, *24*, 608-616.

[61] Keck, M.E.; Welt, T.; Müller, M.B.; Erhardt, A.; Ohl, F.; Toschi, N.; Holsboer, F.; Sillaber I. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology*, **2002**, *43*,101-109.

[62] Löffler S.; Gasca F.; Richter L.; Leipscher U.; Trillenberg P.; Moser A. The effect of repetitive transcranial magnetic stimulation on monoamine outflow in the nucleus accumbens shell in freely moving rats. *Neuropharmacology*, **2012** ,*63*(5), 898-904.

[63] Erhardt A.; Sillaber I.; Welt .; Müller M.B.; Singewald N.; Keck M.E. Repetitive transcranial magnetic stimulation increases the release of dopamine in the nucleus accumbens shell of morphine-sensitized rats during abstinence. *Neuropsychopharmacology*, **2004**, *29*(11), 2074-80.

[64] Fleischmann, A.; Sternheim, A.; Etgen, A.M.; L,i C.; Grisaru, N.; Belmaker, R.H. Transcranial magnetic stimulation downregulates beta-adrenoreceptors in rat cortex. *J. Neural. Transm.,* **1996**, *103*,1361-1366.

[65] Goyagi T.; Kimura T.; Nishikawa T.; Tobe Y.; Masaki Y. Beta-adrenoreceptor antagonists attenuate brain injury after transient focal ischemia in rats. *Anesth Analg.* , **2006**, *103*, 658-63.

[66] Müller M.B.; Toschi N.; Kresse A.E.; Post A.; Keck M.E. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology*, **2000**, *23*(2), 205-15.

[67] Yuluğ, B.; Ozan ,E.; Gönül, A.S.; Kilic,E. Brain-derived neurotrophic factor, stress and depression: a minireview. *Brain Res Bull.*, **2009** , *78*(6), 267-9.

[68] Feng , S.F.; Shi, T.Y.; Fan, Y.; Wang ,W.N.; Chen ,Y.C.; Tan Q.R. Long-lasting effects of chronic rTMS to treat chronic rodent model of depression. *Behav. Brain Res.,* **2012**, *232*(1), 245-51.

[69] Keck, M.E.; Engelmann, M.; Müller, M.B.; Henniger, M.S.; Hermann, B.; Rupprecht, R.; Neumann, I.D.; Toschi, N.; Landgraf, R.; Post, A. Repetitive transcranial magnetic stimulation induces active coping strategies and attenuates the neuroendocrine stress response in rats. *J. Psychiatr. Res.*, **2000**, 34, 265-276.

[70] Czeh, B.; Welt, T.; Fischer, A.K.; Erhardt, A.; Schmitt, W.; Müller, M.B.; Toschi, N.; Fuchs, E.; Keck, M.E. Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. *Biol. Psychiatry.,* **2002**, *52*, 1057-1065.

[71] Keck, M.E; Welt, T.; Post, A.; Müller M.B.; Toschi ,N.; Wigger , A.; Landgraf, R.; Holsboer, F.; Engelmann, M. Neuroendocrine and behavioral effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of
antidepressant-like effects. *Neuropsychopharmacology*, **2001**, *24*(4), 337-49.

[72] Wang, H.N.; Wang, L.; Zhang R.G.; Chen Y.C.; Liu ,L.; Gao ,F.; Nie ,H.; Hou, W.G.; Peng , Z.W.; Tan, Q. Anti-depressive mechanism of repetitive transcranial magnetic stimulation in rat: the role of the endocannabinoid system. *J. Psychiatr. Res.,* **2014,** *51*, 79-87.

[73] Ueyama, E.; Ukai,S.; Ogawa, A,; Yamamoto, M.; Kawaguchi, S.; Ishii, R.; Shinosaki, K. Chronic repetitive transcranial magnetic stimulation increases hippocampal
neurogenesis in rats. *Psychiatry Clin. Neurosci*., **2011**, *65*(1), 77-81.

[74] Zhang,Y.; Mao, R.R.; Chen, Z.F.; Tian, M.; Tong, D.L.; Gao, Z.R.; Huang, M.; Li, X.; Zhou,W.H.; Li , C.Y.; Wang , J.; Xu , L.; Qiu, Z. Deep-brain magnetic stimulation promotes adult hippocampal neurogenesis and alleviates stress-related behaviors in mouse models for neuropsychiatric disorders. *Mol. Brain*, **2014**, *11*, 7–11.

[75] Tasset, I.; Drucker-Colín, R.; Peña, J.; Jimena, I.; Montilla, P.; Medina, F.J.; Túnez, I. Antioxidant-like effects and protective action of transcranial magnetic stimulation in depression caused by olfactory bulbectomy. *Neurochem. Res.*, **2010**, 35, 1182-1187.

[76] Peng, C.H,; Chiou, S.H.; Chen, S.J.; Chou,Y.C.; Ku, H.H.; Cheng,C.K.; Yen, C.J.; Tsai,T.H.; Chang,Y.L.; Kao, C.L. Neuro-

protection by Imipramine against lipopolysaccharide-induced apoptosis in hippocampus-derived neural stem cells mediated by activation of BDNF and the MAPK pathway. *Eur. Neuropsychopharmacol*., **2008**, *18*, 128–140.

[77] Hoshaw, B.A.; Malberg, J.E.; Lucki, I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res*., **2005**, *1037*(1-2), 204-8

[78] Tsybko, A.S.; Il'chibaeva, T.V.; Kondaurova, E.M.; Bazovkina, D.V.; Naumenko, V.S. The effect of central administration of the neurotrophic factors BDNF and GDNF on the functional activity and expression of the serotonin 5-HT2A receptors in mice genetically predisposed to depressive-like behavior. *Mol. Biol. (Mosk).,* **2014**, *48*(6), 983-9.

Received: July 11, 2015 Revised: September 08, 2015 Accepted: September 29, 2015