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Therapeutic effects of repetitive transcranial magnetic stimulation in an animal model of Parkinson's disease

Ji Yong Lee[a,b,c,1], Sung Hoon Kim[d,1], Ah-Ra Ko[e], Jin Suk Lee[b], Ji Hea Yu[a,f], Jung Hwa Seo[a,g], Byung Pil Cho[b,h,*], Sung-Rae Cho[a,f,g,i,j,**]

[a]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, South Korea
[b]Department of Anatomy, Yonsei University Wonju College of Medicine, Wonju, South Korea
[c]Graduate School of Medicine, Yonsei University, Seoul, South Korea
[d]Department of Rehabilitation Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea
[e]Life and Health Science, UL, South Korea
[f]Brain Korea 21 plus Project for Medical Science, Yonsei University, Seoul, South Korea
[g]Graduate Program of Nano Science and Technology, Yonsei University, Seoul, South Korea
[h]Institute of Lifestyle Medicine, Yonsei University Wonju College of Medicine, Wonju South Korea
[i]Yonsei Stem Cell Research Center, Avison Biomedical Research Center, Seoul, South Korea
[j]Rehabilitation Institute of Neuromuscular Disease, Yonsei University College of Medicine, Seoul, South Korea

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is used to treat neurological diseases such as stroke and Parkinson's disease (PD). Although rTMS has been used clinically, its underlying therapeutic mechanism remains unclear. The objective of the present study was to clarify the neuroprotective effect and therapeutic mechanism of rTMS in an animal model of PD. Adult Sprague-Dawley rats were unilaterally injected with 6-hydroxydopamine (6-OHDA) into the right striatum. Rats with PD were then treated with rTMS (circular coil, 10 Hz, 20 min/day) daily for 4 weeks. Behavioral assessments such as amphetamine-induced rotational test and treadmill locomotion test were performed, and the dopaminergic (DA) neurons of substantia nigra pas compacta (SNc) and striatum were histologically examined. Expression of neurotrophic/growth factors was also investigated by multiplex ELISA, western blotting analysis and immunohistochemistry 4 weeks after rTMS application. Among the results, the number of amphetamine-induced rotations was significantly lower in the rTMS group than in the control group at 4 weeks post-treatment. Treadmill locomotion was also

*Corresponding author at: Institute of Lifestyle Medicine, Department of Anatomy, Yonsei University Wonju College of Medicine, 172, Ilsan-dong, Wonju 220-702, South Korea.
**Corresponding author at: Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, South Korea. Fax: +82 2 363 2795.
E-mail addresses: bpcho@yonsei.ac.kr (B.P. Cho), srcho918@yuhs.ac (S.-R. Cho).
[1]Both authors contributed equally to this work.

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significantly improved in the rTMS-treated rats. Tyrosine hydroxylase-positive DA neurons and DA fibers in rTMS group rats were greater than those in untreated group in both ipsilateral SNc and striatum, respectively. The expression levels of brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, platelet-derived growth factor, and vascular endothelial growth factor were elevated in both the 6-OHDA-injected hemisphere and the SNc of the rTMS-treated rats. In conclusion, rTMS treatment improved motor functions and survival of DA neurons, suggesting that the neuroprotective effect of rTMS treatment might be induced by upregulation of neurotrophic/growth factors in the PD animal model.

1. Introduction

Parkinson's disease (PD) occurs as a result of degenerating cell death of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). PD is characterized by certain motor disturbances such as resting tremor, bradykinesia, and gait disturbance. Dopamine replacement therapy is an effective medical treatment for the symptomatic improvement of PD. In spite of such effects, fluctuations in abnormal involuntary movement eventually occur in most patients after long-term dopaminergic treatment. Consequently, several studies have investigated various methods other than dopaminergic drugs for PD treatment (Wu et al., 2008).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapeutic device that can alter the excitability of the cerebral cortex or neural network. rTMS has been used to treat neuropsychiatric diseases (Zwanzger et al., 2002; Bentwich et al., 2011; Fitzgerald and Daskalakis, 2011) and stroke (Theilig et al., 2011; Corti et al., 2012). Recently, several clinical trials have revealed that rTMS offers therapeutic benefit for functional recovery in PD (Siebner et al., 1999; Arias-Carrión, 2008; Wu et al., 2008; Yang et al., 2013). rTMS treatment has shown to improve motor function and cognition in patients with PD (Zamir et al., 2012). Additionally, increased DA levels in serum and subcortical areas have been observed following rTMS in both PD patients and experimental animals (Strafella et al., 2001, 2003; Khedr et al., 2007; Choand Strafella, 2009).

On the other hand, the underlying mechanism of rTMS still remains to be elucidated. Recently, several experiments have shown that rTMS has the ability to mediate neuroplasticity by enhancing the expressions of glutamate neurotransmitters and brain-derived neurotrophic factor (BDNF) in rat brains (Müller et al., 2000; Keck et al., 2000; Yue et al., 2009). rTMS did not only activate brain regions in terms of immediate early gene expression, but also increased the expression of BDNF-TrkB signaling in rats and humans (Ji et al., 1998; Hausmann et al., 2000; Doi et al., 2001; Wang et al., 2011). Additionally, rTMS modulated neurotrophic factors such as BDNF, cholecystokinin and neuropetide tyrosine in healthy humans and patients with depression and amyotrophic lateral sclerosis (Angelucci et al., 2004; Yukimasa et al., 2006; Gedge et al., 2012). However, there are few rTMS studies on the effects of various neurotrophic/growth factors in PD.

To clarify the neuroprotective effect of rTMS on SNc DA neurons and the therapeutic mechanism in overall brain after rTMS treatment, the present study investigated motor functions and tyrosine hydroxylase (TH)-immunoreactive DA neurons and DA nerve fibers in the SNc and striatum. In addition, the expression of neurotrophic/growth factors was examined after rTMS application in an animal model of PD.

2. Results

2.1. *Effects of rTMS on amphetamine-induced rotation test*

Adult Sprague-Dawley rats were unilaterally injected with 6-hydroxydopamine (6-OHDA) into the right striatum. Two weeks after 6-OHDA injection, rats with PD were treated with rTMS (circular coil, 10 Hz, 20 min/day) daily for 4 weeks (Fig. 1A–C). Functional benefit in rTMS-treated rats on amphetamine-induced rotation behavior was evaluated up to 4 weeks after treatment ($n=12$ each). Whereas untreated group showed continuous augmentation in rotational behavior, the increasing rate of amphetamine-induced rotations was significantly lowered in rTMS-treated rats at 4 weeks after treatment (Fig. 2A). The number of rotations was not significantly different between the rTMS group (387.3 ± 43.4) and the untreated group (319.2 ± 41.3) at 2 weeks post-treatment. However, the number of rotations in the rTMS group (386.9 ± 43.8) was significantly lower than that in the untreated group (549.9 ± 33.6) at 4 weeks post-treatment ($F=5.52$, $p=0.03$).

2.2. *rTMS improved locomotor function in a PD animal model*

Treadmill locomotion test was assessed to determine the effects of the DA lesion on motor functions ($n=12$ each). The rTMS-treated rats showed improvement in locomotor function 2 weeks after treatment (280 ± 25.0 mm), compared with the untreated group (225.1 ± 34.1 mm) (Fig. 2B). The running distance of rTMS-treated rats continuously increased to a final score of 320.2 ± 23.1 mm throughout the treatment period, while the distance of untreated groups maintained to the score of 230 ± 35.5 mm at 4 weeks post-treatment ($F=3.56$, $p=0.04$), implying that rTMS induced motor improvements in the PD rats.