Review Exp Ther Med. 2023 Aug 1;26(3):444. doi: 10.3892/etm.2023.12143.
eCollection 2023 Sep.

Enhancement of neural regeneration as a therapeutic strategy for Alzheimer's disease (Review)

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Abstract

Alzheimer's disease (AD), the most common cause of dementia worldwide, has gradually become a global health concern for society and individuals with the process of global ageing. Although extensive research has been carried out on AD, the etiology and pathological mechanism of the disease are still unclear, and there is no specific drug to cure or delay AD progression. The exploration of enhancing nerve regeneration in AD has gradually attracted increasing attention. In the current review, the existing therapeutic strategies were summarized to induce nerve regeneration which can increase the number of neurons, and improve the survival of neurons, the plasticity of synapses and synaptic activity. The strategies include increasing neurotrophic expression (such as brain-derived neurotrophic factor and nerve growth factor), inhibiting acetylcholinesterase (such as donepezil, tacrine, rivastigmine and galanthamine), elevating histone deacetylase levels (such as RGFP-966, Tasquinimod, CM-414 and 44B), stimulating the brain by physiotherapy (such as near-infrared light, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation) and transplanting exogenous neural stem cells. However, further evaluations need to be performed to determine the optimal treatment. The present study reviews recent interventions for enhancing adult neurogenesis and attempts to elucidate their mechanisms of action, which may provide a theoretical basis for inducing nerve regeneration to fight against AD.

Keywords: Alzheimer's disease; brain stimulation; inhibitors; nerve regeneration; neurotrophin; transplantation.

Figures

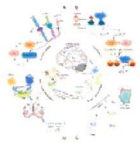

Figure 1 Different interventions enhance nerve regeneration...

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J Gerontol A Biol Sci Med Sci. 2019 Aug 16;74(9):1341-1350. doi: 10.1093/gerona/gly221.

Synergistic Effects of Mesenchymal Stem Cell Transplantation and Repetitive Transcranial Magnetic Stimulation on Promoting Autophagy and Synaptic Plasticity in Vascular Dementia

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PMID: 30256913 DOI: 10.1093/gerona/gly221

Abstract

Repetitive transcranial magnetic stimulation (rTMS) and mesenchymal stem cells (MSCs) transplantation both showed therapeutic effects on cognition impairment in vascular dementia (VD) model rats. However, whether these two therapies have synergistic effects and the molecular mechanisms remain unclear. In our present study, rats were randomly divided into six groups: control group, sham operation group, VD group, MSC group, rTMS group, and MSC+rTMS group. The VD model rats were prepared using a modified 2VO method. rTMS treatment was implemented at a frequency of 5 Hz, the stimulation intensity for 0.5 Tesla, 20 strings every day with 10 pulses per string and six treatment courses. The results of the Morris water maze test showed that the learning and memory abilities of the MSC group, rTMS group, and MSC+rTMS group were better than that of the VD group, and the MSC+rTMS group showed the most significant effect. The protein expression levels of brain-derived neurotrophic factor, NR1, LC3-II, and Beclin-1 were the highest and p62 protein was the lowest in the MSC+rTMS group. Our findings demonstrated that rTMS could further enhance the effect of MSC transplantation on VD rats and provided an important basis for the combined application of MSC transplantation and rTMS to treat VD or other neurological diseases.

Keywords: Autophagy; Brain-derived neurotrophic factor; Marrow mesenchymal stem cells; Repetitive transcranial magnetic stimulation; Vascular dementia.

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Tissue Eng Regen Med. 2020 Feb;17(1):67-80. doi: 10.1007/s13770-019-00233-8. Epub 2020 Jan 22.

Combination of Human Mesenchymal Stem Cells and Repetitive Transcranial Magnetic Stimulation Enhances Neurological Recovery of 6-Hydroxydopamine Model of Parkinsonian's Disease

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Affiliations

PMID: 31970698 PMCID: PMC6992828 DOI: 10.1007/s13770-019-00233-8

Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) has been in use for the treatment of various neurological diseases, including depression, anxiety, stroke and Parkinson's disease (PD), while its underlying mechanism is stills unclear. This study was undertaken to evaluate the potential synergism of rTMS treatment to the beneficial effect of human mesenchymal stem cells (hMSCs) administration for PD and to clarify the mechanism of action of this therapeutic approach.

Methods: The neuroprotective effect in nigral dopamine neurons, neurotrophic/growth factors and anti-/pro-inflammatory cytokine regulation, and functional recovery were assessed in the rat 6-hydroxydopamine (6-OHDA) model of PD upon administration of hMSCs and rTMS.

Results: Transplanted hMSCs were identified in the substantia nigra, and striatum. Enhancement of the survival of SN dopamine neurons and the expression of the tyrosine hydroxylase protein were observed in the hMSCs + rTMS compared to that of controls. Combination therapy significantly elevated the expression of several key neurotrophic factors, of which the highest expression was recorded in the rTMS + hMSC group. In addition, the combination therapy significantly upregulated IL-10 expression while decreased IFN-γ and TNF-α production in a synergistic manner. The treadmill locomotion test (TLT) revealed that motor function was improved in the rTMS + hMSC treatment with synergy.

Conclusion: Our findings demonstrate that rTMS treatment and hMSC transplantation could synergistically create a favorable microenvironment for cell survival within the PD rat brain, through alteration of soluble factors such as neurotrophic/growth factors and anti-/pro-inflammatory cytokines related to neuronal protection or repair, with preservation of DA neurons and improvement of motor functions.

Keywords: Anti-/pro-inflammatory cytokine; Mesenchymal stem cell; Neurotrophic factor; Parkinson's disease; Repetitive transcranial magnetic stimulation.

Figures

Review Cell Transplant. 2016;25(5):863-82. doi: 10.3727/096368916X690511. Epub 2016 Jan 18.

Induction of Neurorestoration From Endogenous Stem Cells

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PMID: 26787093 DOI: 10.3727/096368916X690511

Free article

Abstract

Neural stem cells (NSCs) persist in the subventricular zone lining the ventricles of the adult brain. The resident stem/progenitor cells can be stimulated in vivo by neurotrophic factors, hematopoietic growth factors, magnetic stimulation, and/or physical exercise. In both animals and humans, the differentiation and survival of neurons arising from the subventricular zone may also be regulated by the trophic factors. Since stem/progenitor cells present in the adult brain and the production of new neurons occurs at specific sites, there is a possibility for the treatment of incurable neurological diseases. It might be feasible to induce neurogenesis, which would be particularly efficacious in the treatment of striatal neurodegenerative conditions such as Huntington's disease, as well as cerebrovascular diseases such as ischemic stroke and cerebral palsy, conditions that are widely seen in the clinics. Understanding of the molecular control of endogenous NSC activation and progenitor cell mobilization will likely provide many new opportunities as therapeutic strategies. In this review, we focus on endogenous stem/progenitor cell activation that occurs in response to exogenous factors including neurotrophic factors, hematopoietic growth factors, magnetic stimulation, and an enriched environment. Taken together, these findings suggest the possibility that functional brain repair through induced neurorestoration from endogenous stem cells may soon be a clinical reality.

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Neurorestoration after stroke

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Affiliations

PMID: 27132523 PMCID: PMC4916840 DOI: 10.3171/2016.2.FOCUS15637

Abstract

Recent advancements in stem cell biology and neuromodulation have ushered in a battery of new neurorestorative therapies for ischemic stroke. While the understanding of stroke pathophysiology has matured, the ability to restore patients' quality of life remains inadequate. New therapeutic approaches, including cell transplantation and neurostimulation, focus on reestablishing the circuits disrupted by ischemia through multidimensional mechanisms to improve neuroplasticity and remodeling. The authors provide a broad overview of stroke pathophysiology and existing therapies to highlight the scientific and clinical implications of neurorestorative therapies for stroke.

Keywords: BCI = brain-computer interface; G-CSF = granulocyte colony-stimulating factor; MSC = mesenchymal stem cell; NPC = neural progenitor cell; NSC = neural stem cell; NT2N = Ntera2/D1 neuron-like; PSD-95 = postsynaptic density-95; RCT = randomized controlled trial; TMS = transcranial magnetic stimulation; brain-computer interface; exogenous stem cells; neuroplasticity; optogenetics; tDCS = transcranial direct current stimulation; tPA = tissue plasminogen activator.

Figures

FIG. 1 Overview of neurorestorative modalities. rTMS...

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Review Neurosci Bull. 2021 May;37(5):735-745. doi: 10.1007/s12264-021-00667-y.
Epub 2021 Apr 19.

Neuromodulation-Based Stem Cell Therapy in Brain Repair: Recent Advances and Future Perspectives

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Affiliations

PMID: 33871821 PMCID: PMC8099989 DOI: 10.1007/s12264-021-00667-y

Abstract

Stem cell transplantation holds a promising future for central nervous system repair. Current challenges, however, include spatially and temporally defined cell differentiation and maturation, plus the integration of transplanted neural cells into host circuits. Here we discuss the potential advantages of neuromodulation-based stem cell therapy, which can improve the viability and proliferation of stem cells, guide migration to the repair site, orchestrate the differentiation process, and promote the integration of neural circuitry for functional rehabilitation. All these advantages of neuromodulation make it one potentially valuable tool for further improving the efficiency of stem cell transplantation.

Keywords: Deep brain stimulation; Neuromodulation; Rehabilitation; Stem cell; Transcranial direct current stimulation; Transcranial magnetic stimulation.

Figures

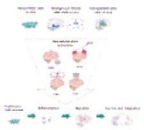

Fig. 1 Neuromodulation techniques used to alter...

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Exp Neurol. 2019 Mar:313:1-9. doi: 10.1016/j.expneurol.2018.12.002. Epub 2018 Dec 4.

Repetitive transcranial magnetic stimulation promotes functional recovery and differentiation of human neural stem cells in rats after ischemic stroke

Jiao-Jiao Peng [1], Rong Sha [1], Ming-Xing Li [1], Lu-Ting Chen [1], Xiao-Hua Han [1], Feng Guo [1], Hong Chen [2], Xiao-Lin Huang [3]

Affiliations

PMID: 30529277 DOI: 10.1016/j.expneurol.2018.12.002

Abstract

Stem cells hold great promise as a regenerative therapy for ischemic stroke by improving functional outcomes in animal models. However, there are some limitations regarding the cell transplantation, including low rate of survival and differentiation. Repetitive transcranial magnetic stimulation (rTMS) has been widely used in clinical trials as post-stroke rehabilitation in ischemic stroke and has shown to alleviate functional deficits following stroke. The present study was designed to evaluate the therapeutic effects and mechanisms of combined human neural stem cells (hNSCs) with rTMS in a middle cerebral artery occlusion (MCAO) rat model. The results showed that human embryonic stem cells (hESCs) were successfully differentiated into forebrain hNSCs for transplantation and hNSCs transplantation combined with rTMS could accelerate the functional recovery after ischemic stroke in rats. Furthermore, this combination not only significantly enhanced neurogenesis and the protein levels of brain-derived neurotrophic factor (BDNF), but also rTMS promoted the neural differentiation of hNSCs. Our findings are presented for the first time to evaluate therapeutic benefits of combined hNSCs and rTMS for functional recovery after ischemic stroke, and indicated that the combination of hNSCs with rTMS might be a potential novel therapeutic target for the treatment of stroke.

Keywords: Brain-derived neurotrophic factor; Differentiation; Functional recovery; Human neural stem cells; Ischemic stroke; Repetitive transcranial magnetic stimulation; Transplantation.

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Anat Cell Biol. 2015 Jun;48(2):104-13. doi: 10.5115/acb.2015.48.2.104. Epub 2015 Jun 26.

The effects of repetitive transcranial magnetic stimulation on proliferation and differentiation of neural stem cells

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Affiliations

PMID: 26140221 PMCID: PMC4488638 DOI: 10.5115/acb.2015.48.2.104

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a new method for treating many neurological conditions; however, the exact therapeutic mechanisms behind rTMS-induced plasticity are still unknown. Neural stem and progenitor cells (NS/PCs) are active players in brain regeneration and plasticity but their behavior in the context of rTMS therapy needs further elucidation. We aimed to evaluate the effects of rTMS on proliferation and differentiation of NS/PCs in the subventricular zone (SVZ) of adult mouse brain. Adult male mice (n=30) were divided into rTMS (1-Hz and 30-Hz) and sham groups and treated for 7 or 14 consecutive days. Harvested NS/PCs from the SVZ were cultured in the neurosphere assay for 8 days and the number and size of the resulting neurospheres as well as their in vitro differentiation capacity were evaluated. After one week of rTMS treatment at 1-Hz and 30-Hz compared with sham stimulation, the mean neurosphere forming frequency per brain was not different while this measure significantly increased after two weeks ($P<0.05$). The mean neurosphere diameter in 1-Hz treatment paradigm was significantly larger compared with sham stimulation at both 1 and 2 weeks. In contrast, 30-Hz treatment paradigm resulted in significantly larger neurospheres only after 2 weeks. Importantly, rTMS treatment at both frequencies increased neuronal differentiation of the harvested NS/PCs. Furthermore, one week in vitro rTMS treatment of NS/PCs with both 1-Hz and 30-Hz increased NS/PCs proliferation and neuronal differentiation. It is concluded that both 1-Hz and 30-Hz rTMS treatment increase NS/PCs proliferation and neuronal differentiation.

Keywords: Neural stem and progenitor cells; Neurosphere assay; Proliferation; Subventricular zone; rTMS.

Figures

J Huazhong Univ Sci Technolog Med Sci. 2015 Oct;35(5):766-772. doi: 10.1007/s11596-015-1505-3. Epub 2015 Oct 22.

Repetitive magnetic stimulation promotes neural stem cells proliferation by upregulating MiR-106b in vitro

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Affiliations

PMID: 26489637 DOI: 10.1007/s11596-015-1505-3

Abstract

Neural stem cells (NSCs) proliferation can be influenced by repetitive transcranial magnetic stimulation (rTMS) in vivo via microRNA-106b-25 cluster, but the underlying mechanisms are poorly understood. This study investigated the involvement of microRNA-106b-25 cluster in the proliferation of NSCs after repetitive magnetic stimulation (rMS) in vitro. NSCs were stimulated by rMS (200/400/600/800/1000 pulses per day, with 10 Hz frequency and 50% maximum machine output) over a 3-day period. NSCs proliferation was detected by using ki-67 and EdU staining. Ki-67, p21, p57, cyclinD1, cyclinE, cyclinA, cdk2, cdk4 proteins and miR-106b, miR-93, miR-25 mRNAs were detected by Western blotting and qRT-PCR, respectively. The results showed that rMS could promote NSCs proliferation in a dose-dependent manner. The proportions of ki-67+ and Edu+ cells in 1000 pulses group were 20.65% and 4.00%, respectively, significantly higher than those in control group (9.25%, 2.05%). The expression levels of miR-106b and miR-93 were significantly upregulated in 600-1000 pulses groups compared with control group ($P<0.05$ or 0.01 for all). The expression levels of p21 protein were decreased significantly in 800/1000 pulses groups, and those of cyclinD1, cyclinA, cyclinE, cdk2 and cdk4 were obviously increased after rMS as compared with control group ($P<0.05$ or 0.01 for all). In conclusion, our findings suggested that rMS enhances the NSCs proliferation in vitro in a dose-dependent manner and miR-106b/p21/cdks/cyclins pathway was involved in the process.

Keywords: EdU; cyclin-dependent kinase; cyclin-dependent kinase inhibitor; ki67; microRNA-106b; neural stem cells; repetitive magnetic stimulation.

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Neuroscience. 2023 Aug 1:524:1-10. doi: 10.1016/j.neuroscience.2022.09.013. Epub 2022 Sep 15.

Repetitive Transcranial Magnetic Stimulation Improves Depression-like Behavior in Rats by Promoting Neural Stem Cell Proliferation and Differentiation

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PMID: 36116556 DOI: 10.1016/j.neuroscience.2022.09.013

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a novel non-invasive neuromodulation technique with neuroprotective properties and is used to treat depression. However, the underlying mechanism of action remains unclear. In this study, we examined the possible mechanism mediating the antidepressant effect of rTMS using animal experiments. Specific pathogen-free rats were treated with rTMS after exposure to social isolation combined with chronic unpredictable mild stress (CUMS). After four weeks of CUMS, the rats exhibited a significant decrease in spatial working memory assessed using open-field testing, a general loss of interest assessed with the sucrose preference test, and a significant reduction in spatial recognition memory ability assessed using the Y-maze. These behavioral deficits were accompanied by decreased numbers of astrocytes in the hippocampus, decreased expression of glial fibrillary acidic protein (GFAP), increased numbers of neural stem cells (NSCs), and increased expression of nestin protein. These results indicated that neuron damage occurred in the depression-like rats. After rTMS intervention, the depression-like behavior was alleviated significantly, and the numbers of NSCs and astrocytes, as well as the expression of GFAP and nestin proteins, returned to normal levels. Overall, it is likely that attenuation of NSC proliferation and differentiation into astrocytes produced a neuroprotective effect on hippocampal neurons, which might partly explain the mechanism by which rTMS alleviates depression.

Keywords: GFAP; Hippocampus; Nestin; Neurprotection; rTMS.

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Exp Ther Med. 2021 Sep;22(3):1037. doi: 10.3892/etm.2021.10469. Epub 2021 Jul 19.

Repetitive transcranial magnetic stimulation increases neurological function and endogenous neural stem cell migration via the SDF-1α/CXCR4 axis after cerebral infarction in rats

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Affiliations

PMID: 34373723 PMCID: PMC8343462 DOI: 10.3892/etm.2021.10469

Abstract

Neural stem cell (NSC) migration is closely associated with brain development and is reportedly involved during recovery from ischaemic stroke. Chemokine signalling mediated by stromal cell-derived factor 1α (SDF-1α) and its receptor CXC chemokine receptor 4 (CXCR4) has been previously documented to guide the migration of NSCs. Although repetitive transcranial magnetic stimulation (rTMS) can increase neurological function in a rat stroke model, its effects on the migration of NSCs and associated underlying mechanism remain unclear. Therefore, the present study investigated the effects of rTMS on ischaemic stroke following middle cerebral artery occlusion (MCAO). All rats underwent rTMS treatment 24 h after MCAO. Neurological function, using modified Neurological Severity Scores and grip strength test and NSC migration, which were measured using immunofluorescence staining, were analysed at 7 and 14 days after MCAO, before the protein expression levels of the SDF-1α/CXCR4 axis was evaluated using western blot analysis. AMD3100, a CXCR4 inhibitor, was used to assess the effects of SDF-1α/CXCR4 signalling. In addition, neuronal survival was investigated using Nissl staining at 14 days after MCAO. It was revealed that rTMS increased the neurological recovery of rats with MCAO, facilitated the migration of NSC, augmented the expression levels of the SDF-1α/CXCR4 axis and decreased neuronal loss. Furthermore, the rTMS-induced positive responses were significantly abolished by AMD3100. Overall, these results indicated that rTMS conferred therapeutic neuroprotective properties, which can restore neurological function after ischaemic stroke, in a manner that may be associated with the activation of the SDF-1α/CXCR4 axis.

Keywords: neural stem cells migration; repetitive transcranial magnetic stimulation; stromal cell-derived factor 1α/CXC chemokine receptor 4; transient focal cerebral ischaemia.

Figures

Cell Transplant. 2019 May;28(5):568-584. doi: 10.1177/0963689719834870. Epub 2019 Mar 4.

Repetitive Transcranial Magnetic Stimulation Promotes Neural Stem Cell Proliferation and Differentiation after Intracerebral Hemorrhage in Mice

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Affiliations

PMID: 30832493 PMCID: PMC7103604 DOI: 10.1177/0963689719834870

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a physical treatment applied during recovery after intracerebral hemorrhage (ICH). With in vivo and in vitro assays, the present study sought to investigate how rTMS influences neural stem cells (NSCs) after ICH and the possible mechanism. Following a collagenase-induced ICH, adult male C57BL/6 J mice were subjected to rTMS treatment every 24 h for 5 days using the following parameters: frequency, 10 Hz; duration, 2 s; wait time, 5.5 s; 960 trains (500 μV/div, 5 ms/div, default setting). Brain water content and neurobehavioral score were assessed at days 1, 3, and 5 after ICH. The proliferation and differentiation of NSCs were observed using immunofluorescence staining for Nestin, Ki-67, DCX, and GFAP on day 3 after ICH, and rTMS treatment with the same parameters was applied to NSCs in vitro. We found that rTMS significantly reduced brain edema and alleviated neural functional deficits. The mice that underwent ICH recovered faster after rTMS treatment, with apparent proliferation and neuronal differentiation of NSCs and attenuation of glial differentiation and GFAP aggregation. Accordingly, proliferation and neuronal differentiation of isolated NSCs were promoted, while glial differentiation was reduced. In addition, microarray analysis, western blotting assays, and calcium imaging were applied to initially investigate the potential mechanism. Bioinformatics showed that the positive effect of rTMS on NSCs after ICH was largely related to the MAPK signaling pathway, which might be a potential hub signaling pathway under the complex effect exerted by rTMS. The results of the microarray data analysis also revealed that Ca^{2+} might be the connection between physical treatment and the MAPK signaling pathway. These predictions were further identified by western blotting analysis and calcium imaging. Taken together, our findings showed that rTMS after ICH exhibited a restorative effect by enhancing the proliferation and neuronal differentiation of NSCs, potentially through the MAPK signaling pathway.

Keywords: differentiation; intracerebral hemorrhage; mitogen-activated protein kinase; neural stem cell; proliferation; repetitive transcranial magnetic stimulation.

Figures

J Neurosci. 2023 Apr 26;43(17):3042-3060. doi: 10.1523/JNEUROSCI.2226-22.2023.
Epub 2023 Mar 28.

Microglial Cytokines Mediate Plasticity Induced by 10 Hz Repetitive Magnetic Stimulation

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Affiliations

PMID: 36977586 PMCID: PMC10146500 DOI: 10.1523/JNEUROSCI.2226-22.2023

Abstract

Microglia, the resident immune cells of the CNS, sense the activity of neurons and regulate physiological brain functions. They have been implicated in the pathology of brain diseases associated with alterations in neural excitability and plasticity. However, experimental and therapeutic approaches that modulate microglia function in a brain region-specific manner have not been established. In this study, we tested for the effects of repetitive transcranial magnetic stimulation (rTMS), a clinically used noninvasive brain stimulation technique, on microglia-mediated synaptic plasticity; 10 Hz electromagnetic stimulation triggered a release of plasticity-promoting cytokines from microglia in mouse organotypic brain tissue cultures of both sexes, while no significant changes in microglial morphology or microglia dynamics were observed. Indeed, substitution of tumor necrosis factor α (TNFα) and interleukin 6 (IL6) preserved synaptic plasticity induced by 10 Hz stimulation in the absence of microglia. Consistent with these findings, *in vivo* depletion of microglia abolished rTMS-induced changes in neurotransmission in the mPFC of anesthetized mice of both sexes. We conclude that rTMS affects neural excitability and plasticity by modulating the release of cytokines from microglia.**SIGNIFICANCE STATEMENT** Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique that induces cortical plasticity. Despite its wide use in neuroscience and clinical practice (e.g., depression treatment), the cellular and molecular mechanisms of rTMS-mediated plasticity remain not well understood. Herein, we report an important role of microglia and plasticity-promoting cytokines in synaptic plasticity induced by 10 Hz rTMS in organotypic slice cultures and anesthetized mice, thereby identifying microglia-mediated synaptic adaptation as a target of rTMS-based interventions.

Keywords: IL6; TNF; excitatory synaptic plasticity; microglia; microglia depletion; rTMS.

Figures

Int J Mol Sci. 2017 Feb 20;18(2):455. doi: 10.3390/ijms18020455.

High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Improves Functional Recovery by Enhancing Neurogenesis and Activating BDNF/TrkB Signaling in Ischemic Rats

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Affiliations

PMID: 28230741 PMCID: PMC5343989 DOI: 10.3390/ijms18020455

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has rapidly become an attractive therapeutic approach for stroke. However, the mechanisms underlying this remain elusive. This study aimed to investigate whether high-frequency rTMS improves functional recovery mediated by enhanced neurogenesis and activation of brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB) pathway and to compare the effect of conventional 20 Hz rTMS and intermittent theta burst stimulation (iTBS) on ischemic rats. Rats after rTMS were sacrificed seven and 14 days after middle cerebral artery occlusion (MCAO), following evaluation of neurological function. Neurogenesis was measured using specific markers: Ki67, Nestin, doublecortin (DCX), NeuN and glial fibrillary acidic protein (GFAP), and the expression levels of BDNF were visualized by Western blotting and RT-PCR analysis. Both high-frequency rTMS methods significantly improved neurological function and reduced infarct volume. Moreover, 20 Hz rTMS and iTBS significantly promoted neurogenesis, shown by an increase of Ki67/DCX, Ki67/Nestin, and Ki67/NeuN-positive cells in the peri-infarct striatum. These beneficial effects were accompanied by elevated protein levels of BDNF and phosphorylated-TrkB. In conclusion, high-frequency rTMS improves functional recovery possibly by enhancing neurogenesis and activating BDNF/TrkB signaling pathway and conventional 20 Hz rTMS is better than iTBS at enhancing neurogenesis in ischemic rats.

Keywords: BDNF; MCAO; TrkB; neural stem cells; neurological function; rTMS.

Figures

Int J Mol Med. 2018 Dec;42(6):3631-3639. doi: 10.3892/ijmm.2018.3922. Epub 2018 Oct 9.

Repetitive magnetic stimulation promotes the proliferation of neural progenitor cells via modulating the expression of miR-106b

Hua Liu [1], Gaohua Li [2], Chunlian Ma [1], Yanfang Chen [3], Jinju Wang [3], Yi Yang [1]

Affiliations

PMID: 30320352 DOI: 10.3892/ijmm.2018.3922

Abstract

Increasing evidence shows that repetitive transcranial magnetic stimulation (rTMS) promotes neurogenesis and the expression of microRNA (miR)-106b. The present study investigated whether rTMS promotes the proliferation of neural progenitor cells (NPCs) and whether the effect is associated with the expression of miR-106b. NPCs were cultured from the rat hippocampus and exposed to rTMS daily, comprising 1,000 stimuli for 3 days at 10 Hz, with 1.75 T output. The proliferation ability of the NPCs was revealed by EdU staining, and the levels of miR-106b and downstream gene p21 in the NPCs were measured by reverse transcription-quantitative polymerase chain reaction and western blot analyses. For analysis of the mechanism, the NPCs were transfected with Lenti-miR-106b or small interfering RNAs prior to rTMS. The results showed that: i) rTMS increased NPC proliferation, as revealed by the increased proportion of EdU-positive cells; ii) rTMS was able to upregulate the expression of miR-106b and downregulate the level of p21 in NPCs; iii) overexpression of miR-106b further enhanced the effects of rTMS, whereas knockdown of miR-106b had the opposite effects. Taken together, these data indicated that rTMS can promote NPC proliferation by upregulating the expression of miR-106b and possibly inhibiting the expression of p21.

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Front Neurol. 2018 May 7:9:285. doi: 10.3389/fneur.2018.00285. eCollection 2018.

High-Frequency Repetitive Magnetic Stimulation Enhances the Expression of Brain-Derived Neurotrophic Factor Through Activation of Ca^{2+}-Calmodulin-Dependent Protein Kinase II-cAMP-Response Element-Binding Protein Pathway

Ahreum Baek [1 2], Eun Jee Park [3], Soo Yeon Kim [4], Bae-Geun Nam [2 5], Ji Hyun Kim [1], Sang Woo Jun [6], Sung Hoon Kim [1], Sung-Rae Cho [2 5 7 8 9]

Affiliations

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) can be used in various neurological disorders. However, neurobiological mechanism of rTMS is not well known. Therefore, in this study, we examined the global gene expression patterns depending on different frequencies of repetitive magnetic stimulation (rMS) in both undifferentiated and differentiated Neuro-2a cells to generate a comprehensive view of the biological mechanisms. The Neuro-2a cells were randomly divided into three groups-the sham (no active stimulation) group, the low-frequency (0.5 Hz stimulation) group, and high-frequency (10 Hz stimulation) group-and were stimulated 10 min for 3 days. The low- and high-frequency groups of rMS on Neuro-2a cells were characterized by transcriptome array. Differentially expressed genes were analyzed using the Database of Annotation Visualization and Integrated Discovery program, which yielded a Kyoto Encyclopedia of Genes and Genomes pathway. Amphetamine addiction pathway, circadian entrainment pathway, long-term potentiation (LTP) pathway, neurotrophin signaling pathway, prolactin signaling pathway, and cholinergic synapse pathway were significantly enriched in high-frequency group compared with low-frequency group. Among these pathways, LTP pathway is relevant to rMS, thus the genes that were involved in LTP pathway were validated by quantitative real-time polymerase chain reaction and western blotting. The expression of glutamate ionotropic receptor *N*-methyl d-aspartate 1, calmodulin-dependent protein kinase II (CaMKII) δ, and CaMKIIα was increased, and the expression of CaMKIIγ was decreased in high-frequency group. These genes can activate the calcium (Ca^{2+})-CaMKII-cAMP-response element-binding protein (CREB) pathway. Furthermore, high-frequency rMS induced phosphorylation of CREB, brain-derived neurotrophic factor (BDNF) transcription *via* activation of Ca^{2+}-CaMKII-CREB pathway. In conclusion, high-frequency rMS enhances the expression of BDNF by activating Ca^{2+}-CaMKII-CREB pathway in the Neuro-2a cells. These findings may help clarify further therapeutic mechanisms of rTMS.

Keywords: Ca2+–calmodulin-dependent protein kinase II–cAMP-response element-binding protein pathway; Neuro-2a cells; brain-derived neurotrophic factor; high-frequency; low-frequency; repetitive magnetic stimulation.

Figures

PLoS One. 2014 Oct 10;9(10):e109267. doi: 10.1371/journal.pone.0109267. eCollection 2014.

Repetitive transcranial magnetic stimulation promotes neural stem cell proliferation via the regulation of MiR-25 in a rat model of focal cerebral ischemia

Feng Guo [1], Xiaohua Han [1], Jinghui Zhang [2], Xiuxiu Zhao [1], Jicheng Lou [3], Hong Chen [1], Xiaolin Huang [1]

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) has increasingly been studied over the past decade to determine whether it has a therapeutic benefit on focal cerebral ischemia. However, the underlying mechanism of rTMS in this process remains unclear. In the current study, we investigated the effects of rTMS on the proliferation of adult neural stem cells (NSCs) and explored microRNAs (miRNAs) that were affected by rTMS. Our data showed that 10 Hz rTMS significantly increased the proliferation of adult NSCs after focal cerebral ischemia in the subventricular zone (SVZ), and the expression of miR-25 was obviously up-regulated in the ischemic cortex after rTMS. p57, an identified miR-25 target gene that regulates factors linked to NSC proliferation, was also evaluated, and it exhibited down-regulation. To further verify the role of miR-25, rats were injected with a single dose of antagomir-25 and were subjected to focal cerebral ischemia followed by rTMS treatment. The results confirmed that miR-25 could be repressed specifically and could drive the up-regulation of its target gene (p57), which resulted in the inhibition of adult NSC proliferation in the SVZ after rTMS. Thus, our studies strongly indicated that 10 Hz rTMS can promote the proliferation of adult NSCs in the SVZ after focal cerebral ischemia by regulating the miR-25/p57 pathway.

Figures

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Figures

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rTMS Regulates the Balance Between Proliferation and Apoptosis of Spinal Cord Derived Neural Stem/Progenitor Cells

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that uses electromagnetic fields to stimulate the brain. rTMS can restore an impaired central nervous system and promote proliferation of neural stem/progenitor cells (NSPCs), but optimal stimulus parameters and mechanisms underlying these effects remain elusive. The purpose of this study is to investigate the effect of different rTMS stimulus parameters on proliferation and apoptosis of spinal cord-derived NSPCs, the expression of brain-derived neurotrophic factor (BDNF) after rTMS, and the potentially underlying pathways. NSPCs were isolated from mice spinal cord and stimulated by different frequencies (1/10/20 Hz), intensities (0.87/1.24/1.58 T), and number of pulses (400/800/1,500/3,000) once a day for five consecutive days. NSPC proliferation was analyzed by measuring the neurosphere diameter and Brdu staining, apoptosis was detected by cell death enzyme-linked immunosorbent assay (ELISA) and flow cytometry, and NSPC viability was assessed by cell counting kit-8 assay. We found that specific parameters of frequency (1/10/20 Hz), intensity (1.24/1.58 T), and number of pulses (800/1,500/3,000) promote proliferation and apoptosis ($p < 0.05$ for all), but 20 Hz, 1.58 T, and 1,500 pulses achieved the optimal response for the NSPC viability. In addition, rTMS significantly promoted the expression of *BDNF* at the mRNA and protein level, while also increasing Akt phosphorylation (Thr308 and Ser473; $p < 0.05$). Overall, we identified the most appropriate rTMS parameters for further studies on NSPCs *in vitro* and *in vivo*. Furthermore, the effect of magnetic stimulation on NSPC proliferation might be correlated to BDNF/Akt signaling pathway.

Keywords: BDNF; apoptosis; neural stem/progenitor cells; proliferation; rTMS.

Figures