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Neurogenic Effect of Repetitive Transcranial Magnetic Stimulation in Adult Brain

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Basic and clinical research suggests potential therapeutic properties for repetitive transcranial magnetic stimulation (rTMS) in the treatment of stroke and neurodegenerative diseases such as Parkinson's disease (PD) and amyotrophic lateral sclerosis. However, the studies on the basic mechanisms of rTMS are scarce, although the rising number of clinical studies have assumed on its therapeutic effects. Animal studies have been suggested mechanism which of how rTMS affects brain circuits and the causal relation in brain-behavior relationships. In addition, recent studies changed perspective that rTMS led to modulate neurotransmitter release, synaptic efficiency, signaling pathways and gene transcription. Furthermore, a few studies suggest that rTMS induces neurogenesis, neuronal viability and secretion of neuroprotective/neurotrophic molecules. In current review, we focused on the basic foundation of possibility on neurogenesis by rTMS in animal with neurodegenerative disorder such as a PD animal model. **Vascular Neurology 2013;5:16-19**

Key Words Repetitive transcranial magnetic stimulation, Parkinson's disease, Neurogenesis.

Introduction

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a neurological technique for non-invasively inducing motor movement by direct magnetic stimulation of the brain's motor cortex to measure connectivity and excitability.[1-5] It depends on the basic principle of mutual induction, whereby magnetic fields can be converted into electrical energy. If the electric field falls in a conductor, electrical current will consequently flow in brain tissue. The repetitive TMS (rTMS) defines that the stimulus can be repeated for a few seconds at frequencies up to 50 Hz.[6-8] The rTMS can be classified as "high-frequency rTMS" (>1 Hz) or "low-frequency rTMS" (<1 Hz). Although the response to rTMS can vary across individuals,[9] high-frequency rTMS seems to facilitate cortical excitability, whereas low-frequency rTMS can suppress the excitability on the motor cortex.[10,11] Recent studies suggest a potential role of rTMS in different neuropsychiatric diseases and neurodegenerative diseases.[6,7] The rTMS has been popular in various fields including cognitive neuroscience and clinical application.[6-8] The use of rTMS in clinical studies is highly advanced and has been reviewed.[12-14] However, despite its utility, the basic mechanisms of rTMS in the context of pathophysiology of neural functions are still unknown.

Cellular and Molecular Mechanisms of rTMS

There is evidence that rTMS causes changes in neuronal circuits as reflected by behavioral changes in animal models.[12-14] These changes include the release of neurotransmitters, synaptic efficiency, signaling pathways and gene transcription. A possible mechanism is that rTMS induces alteration of gene expression.[14-16] Previous studies support that rTMS modulates the expression of immediate early genes such as c-fos and c-jun.[14-16] These genes are activated transiently and rapidly in response to a variety of cellular stimuli. They represent a standing response mechanism that is activated at the transcription level in the first round of response to stimuli before new proteins are synthesized.[14-16] Another study reported that chronic treatment significantly elevated brain-derived neurotrophic factor (BDNF) messenger ribonucleic acid in the hippocampus and the parietal and piriform cortices.[17] Additionally, rTMS modulated various neurotrophic factors such as BDNF, glial

cell line-derived growth factor (GDNF), nerve growth factor (NGF), platelet-derived growth factor, vascular endothelial growth factor, cholesystokinin and neuropetide tyrosine in healthy humans and patients with depression, amyotrophic lateral sclerosis and Parkinson's disease (PD) rat model.[18-21] Effects on neurotrophic factors could possibly explain preliminary findings of neuroprotective and neurotrophic effects of rTMS on degenerated dopaminergic neurons of substantia nigra (SN) by 6-hydroxydopamine (6-OHDA) in PD rats and mossy fiber sprouting in the hippocampus following chronic rTMS.[21,22]

Neurogenesis in the Adult Brain

The adult brain contains two neurogenic regions, the subventricular zone (SVZ) and the subgranular zone (SGZ) in the hippocampus.[23-27] The SVZ contains the largest pool of neural progenitor cells (NPCs) and neural stem cells (NSCs) in the adult brain of all mammals.[24-27] In rodents, the adult SVZ contains four cell types defined by their morphology, ultrastructure, molecular markers and electrophysiological properties: 1) migrating neuronal progenitor cells (type A cells), 2) neurogenic astrocytes (type B cells), which can be visualized by immunostaining for glial fibrillary acidic protein, 3) transit amplifying progenitor cells (type C cells), which proliferate to form fast-dividing NPCs.[24-28] These cells migrate through the rostral migratory stream into the olfactory bulb (OB), where they differentiate and form new interneurons.[29,30] Various events such as pathologic conditions, neurochemical changes in the brain regulate proliferation, migration, and differentiation of these cells. Different growth/trophic factors and cytokines have been identified *in vivo* as modulators of the numeric expansion and as fate determinants of NSCs, such as epidermal growth factor, transforming growth factor-α, fibroblast growth factor-2, NGF, BDNF, GDNF, insulin-like growth factor-1, erythropoietin and so on.[24-26,31] Previous studies in various animal disease models have also shown that the SVZ can respond to insults in the adult brain by producing new progenitor cells that can migrate to sites that have been affected by neurodegenerative disease or brain injury.[26,31] Progenitor cell production, cytokine levels and migratory proteins are upregulated in the SVZ of epilepsy and stroke, leading to an increase in the number of newly generated neurons. By contrast, there are fewer proliferating cells in the SVZ of Alzheimer's disease and PD.[26,31]

Neurogenesis in PD

Many factors including trophic factors have been identified to regulate proliferation, differentiation and migration in adult NSCs. Among these factors, dopamine plays a key role in regulation of adult NSCs in PD, because the characteristic features in this disease are the degeneration of dopaminergic neurons and the loss of dopaminergic innervation to the striatum and SVZ. Generally, precursor cell proliferation in SVZ is decreased in the PD brain. It has been reported that the numbers of proliferating cell nuclear antigen (PCNA)-expressing cells in the SVZ as well as nestin-positive precursor cells in the OB were decreased in post-mortem brain tissue of PD patients.[32] Furthermore, it has been reported that the numbers of nestin-positive cells and βIII tubulin-positive cells decreased in the dentate gyrus of PD patients and PD patients with dementia.[32] In adult mice, dopaminergic afferents project to the SVZ and SGZ, ending in close proximity to precursor cells.[32] In the SVZ, most cells surrounding the dopaminergic fibers are reported to express the epidermal growth factor receptor, and dopaminergic fibers mainly project towards progenitor cells.[32] In adult mice, acute administration of 1-methy1-4-pheny1-1,2,3,6-tetrahydropyridine (MPTP) reduces the number of proliferating cells in the SVZ.[32] It has been shown that in adult mice, MPTP affects the population of dividing progenitor cells, resulting in a decrease in migrating neuroblasts, and eventually in fewer newborn neurons in the OB. Furthermore, it has been shown that dopaminergic denervation decreases the actual number of cycling cells, as measured by the expression of the proliferation marker, PCNA in the SGZ.[32] This is probably due to the loss of dopaminergic input of the hippocampus. Later studies showed that MPTP administration paradigms could result in apoptosis of migrating neuroblasts.[33,34] Several studies have also shown that administration of 6-OHDA can lead to a decrease in proliferation of SVZ precursors,[32,35,36] whereas other studies reported that an increase in SVZ proliferation has been shown after 6-OHDA administration in rats.[37-39] Taken together, dopamine depletion induced by different toxins in different animal models gives a variable outcome on the proliferation of NSCs in the SVZ. Dopamine might play a key role on the proliferation of precursor cells in the SVZ of rodents, resulting in an increase in newborn interneurons in the OB.

Effects of rTMS on Neurogenesis

Previous studies have suggested that long-term rTMS treatments induce an *in situ* differentiation of SVZ-derived precursors to dopamine-producing neurons in PD rats with unilateral 6-OHDA lesions of the SN.[39,40] In behavioral experiments, there was a significant reduction of amphetamine-induced rotations in animals receiving the rTMS. The number of new dopaminergic cells was correlated with improvement of locomotor function. Patch clamp studies suggested that a small percentage of SVZ-derived dopaminergic cells exhibited the electrophysiological properties of mature dopaminergic neurons and presented spontaneous postsynaptic potentials.[39] In addition, chronic rTMS treatment may be related to an increase in the cell proliferation in the hippocampus. It modu-

lates the signaling pathway of extracellular single-regulated kinases, and increase BDNF protein expression in the hippocampus in mice with depression.[41,42] In stroke models, the effect of rTMS on neurogenesis has not been well known. Previous studies have been demonstrated that cerebral ischemia increases neurogenesis both in the SGZ and in the SVZ of the adult brain.[43-45] Neuronal precursors of the SVZ migrate to the ischemic zone of the adjacent striatum, and to the ischemic zone of the cerebral cortex where the damaged neurons are differentiated and replaced.[43-45] This increase might have been associated with the activation of the NMDA receptor.[46] However, the mechanism of rTMS-mediated effect on neurogenesis in post-stroke brain still remains to be elucidated.

Conclusion

Recently, experimental evidences suggest that rTMS induces changes in neurotransmitter release, synaptic efficiency, signaling pathways and gene transcription in healthy and pathologic brain. Furthermore, recent studies suggest that rTMS induces neurogenesis, neuronal viability and secretion of molecules related with neurorestoration such as neurogenesis, angiogenesis in animal models and patients with neurodegenerative disease. It is a new possibility that rTMS represents a new strategy to regenerate the central nervous system by enhancing neurogenesis in adult brain. A detailed understanding of the factors governing adult neurogenesis *in vivo* may ultimately lead to elegant cell therapies for PD and other neurodegenerative disorders by mobilizing endogenous NSCs to replace degenerated neurons. Finally, we should elucidate how rTMS affects the neurobiological change in the brain.

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