REVIEW PAPER

Repetitive Transcranial Magnetic Stimulation of the Brain After Ischemic Stroke: Mechanisms from Animal Models

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Abstract

Stroke is a common cerebrovascular disease with high morbidity, mortality, and disability worldwide. Post-stroke dysfunction is related to the death of neurons and impairment of synaptic structure, which results from cerebral ischemic damage. Currently, transcranial magnetic stimulation (TMS) techniques are available to provide clinically effective interventions and quantitative diagnostic and prognostic biomarkers. The development of TMS has been 40 years and a range of repetitive TMS (rTMS) protocols are now available to regulate neuronal plasticity in many neurological disorders, such as stroke, Parkinson disease, psychiatric disorders, Alzheimer disease, and so on. Basic studies in an animal model with ischemic stroke are significant for demonstrating potential mechanisms of neural restoration induced by rTMS. In this review, the mechanisms were summarized, involving synaptic plasticity, neural cell death, neurogenesis, immune response, and blood–brain barrier (BBB) disruption in vitro and vivo experiments with ischemic stroke models. Those findings can contribute to the understanding of how rTMS modulated function recovery and the exploration of novel therapeutic targets.

Graphical Abstract

The mechanisms of rTMS in treating ischemic stroke from animal models. rTMS can prompt synaptic plasticity by increasing NMDAR, AMPAR and BDNF expression; rTMS can inhibit pro-inflammatory cytokines TNF and facilitate the expression of anti-inflammatory cytokines IL-10 by shifting astrocytic phenotypes from A1 to A2, and shifting microglial phenotypes from M1 to M2; rTMS facilitated the release of angiogenesis-related factors TGFβ and VEGF in A2 astrocytes, which can contribute to vasculogenesis and angiogenesis; rTMS can suppress apoptosis by increasing Bcl-2 expression and inhibiting Bax, caspase-3 expression; rTMS can also suppress pyroptosis by decreasing caspase-1, IL-1β, ASC, GSDMD and NLRP1 expression. rTMS, repetitive transcranial magnetic stimulation; NMDAR, N-methyl-D-aspartic acid receptors; AMPAR:

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α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; GSDMD: cleaved Caspase-1 cleaves Gasdermin D; CBF: cerebral blood flow.
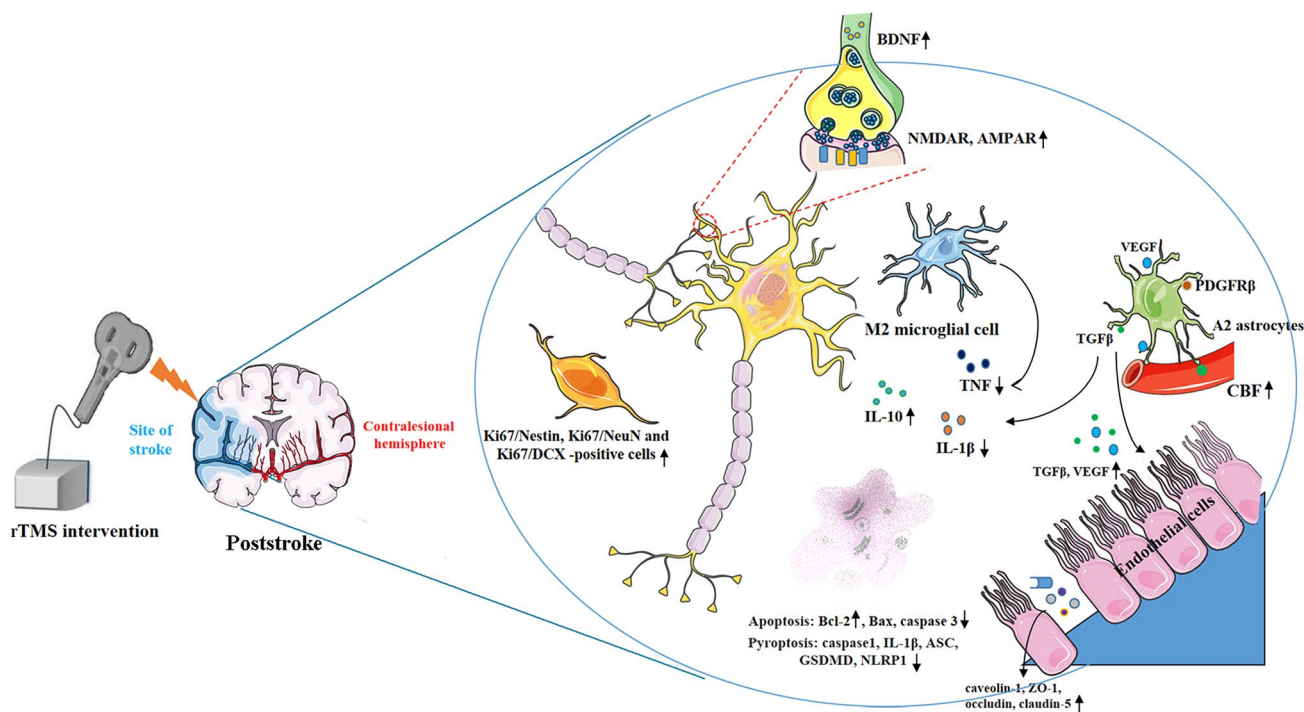
Keywords rTMS · Synaptic plasticity · Ischemic stroke · Neurogenesis · Blood–brain barrier

Introduction

Stroke is a common cerebrovascular disease with high morbidity, mortality, and disability worldwide. Each year, there were 13.7 million stroke cases worldwide, 5.5 million of whom die and as many suffered permanent loss of function due to debilitation (Collaborators 2019). As reported by the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), stroke was the second-ranked leading cause of disability-adjusted life-years (DALYs) in both age groups 50–74 years and 75 years (Diseases and Injuries 2020). The clinical characteristics of stroke patients include dysfunction of cognitive and motor, language disorders, pain, as well as negative mood, which finally impacts the daily life and social ability in patients (Aras et al. 2020; Scuteri et al. 2020; Lodha et al. 2021; Sadlonova et al. 2021). Thus, stroke carries a huge financial burden on individuals and society because of the requirement of full-time care and hospitalization for stroke patients with severe symptoms.

In the clinic, the exploration of effective strategies for treating stroke has gained the focus of world attention. Tissue plasminogen activator is the only existing effective therapy for acute ischemic stroke. Its application is restricted

because of a narrow time window (National Institute of Neurological and Stroke rt 1995). There are no effective therapies to restore function of patients via reversing the impaired brain tissue during the recovery period of stroke. Currently, the best management of stroke is to lower initial impact, avoid further development of the complication, and facilitate the maximization of functional ability by extensive physiotherapy. Thereby, it is an urgent problem to explore an effective and safe treatment for improving functional dysfunction after stroke.

Recently, non-invasive brain stimulation (NIBS) is of great current interest, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and motor cortex stimulation (MCS). rTMS is an indolent strategy used to stimulate the brain regions through the intact skull using magnetic fields (Hallett 2007). As a beneficial neurorehabilitative strategy, it can increase functional recovery both in the acute and subacute phases of ischemic stroke patients (Kim et al. 2014; Blesneag et al. 2015; Tosun et al. 2017). It is effective to improve locomotor deficiency and daily activities, reduce depression and anxiety, and alleviate dysphagia in stroke patients (Frey et al. 2020; Pitts et al. 2020).

According to the stimulation frequency, the effect caused by TMS or rTMS on concurrent cerebral areas is either exciting or inhibiting (Chervyakov et al. 2018; Kim and Yim 2018; Du et al. 2019). Commonly, high-frequency (HF) stimulation (> 5 Hz) induces facilitatory effects, whereas low-frequency (LF) stimulation (≤ 1 Hz) produces inhibitory effects. Theta burst stimulation (TBS) is the HF TMS protocol and is based on the endogenous neural theta rhythm (5 Hz) (Wang et al. 2019). The TBS paradigm includes continuous TBS (cTBS) and intermittent TBS (iTBS). The cTBS typically causes a depressive effect on cortical excitability and the trains of bursts are delivered continuously for 20–40 s. ITBS generally results in a facilitatory effect and its trains are delivered for only 2–8 s pauses (Cardenas-Morales et al. 2010). Individual motor performance depends on the degree of cortical spinal tract (CST) damage, interhemispheric connectivity, and motor cortex excitability (Volz et al. 2015). Normalization of contralesional intracortical excitability, the integrity of ipsilesional CST, and activation of the ipsilesional hemisphere were significantly related to post-stroke motor recovery by rTMS over different cerebral regions (Ameli et al. 2009; Mello et al. 2015; Li et al. 2016).

The beneficial effect of TMS has been observed in an ischemic animal model, including reduced neurological scores, motor threshold (MT), and infarct areas in rats (Feng et al. 2005). By using resting-state functional magnetic resonance imaging, HF rTMS stimulation over the ipsilesional sensorimotor cortex and affected limb increased regional brain activities in the sensorimotor cortex of the ipsilateral hemisphere, whereas decreased brain activities in the sensorimotor cortex of the contralateral hemisphere (Gao et al. 2020). The effects of HF rTMS over the ipsilesional hemisphere are associated with serval molecular mechanisms, including ischemic tolerance, neurogenesis, angiogenesis, anti-apoptosis, inflammation, injury response, or neuroplasticity (Boonzaier et al. 2018; Caglayan et al. 2019). Summarizing basic research findings contributes to the understanding of how rTMS modulated function recovery and the exploration of novel therapeutic targets.

Search Strategy

In this Narrative Review, the relevant abstracts and articles published from inception to June 2022 were searched from the MEDLINE (PubMed), EMBASE, Web of Science. The search terms were (transcranial magnetic stimulation or theta-burst stimulation) and (stroke or cerebral ischemia or ischemic stroke) and the concerned disease is ischemic stroke. The studies in which objects were patients were excluded.

The Effect of rTMS on Changes of Synaptic Plasticity

Synaptic plasticity plays an important role in TMS-induced function recovery after stroke. As reported by a previous study, the dendritic density, total dendritic length, and the number of dendritic branching points were remarkably increased in the undamaged motor cortex after TMS intervention (Mei et al. 2006). Post-synaptic density and synaptic curvatures also significantly increased, whereas the synapse cleft width was significantly lowered (Mei et al. 2006). In the photothrombotic (PT) rat model, rTMS over the ipsilesional primary motor cortex (M1) significantly alleviated neuronal degeneration and synaptic loss in the cortical region surrounding infarct tissue, of which mechanisms were related to inhibiting overexpression of pro-inflammatory cytokines, reactive micro/astrogliosis, oxidative neuronal damage, and oxidative stress (Hong et al. 2020). Thus, TMS can induce significant changes in the structure, number, and function of synapses after stroke.

The rTMS can induce synaptic plasticity by regulating α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and N-methyl-D-aspartate-receptor (NMDAR) in an animal model with stroke. The number and subunit composition of those receptors are not static but change in response to synaptic strength, sensory experiences or neuronal activity (Greger et al. 2002; Paoletti et al. 2013). AMPARs are tetrameric assemblies of subunits GluR1-4, and the majority are GluR1/2 and GluR2/3 heteromers (Hanley 2014). Most neuronal AMPARs contain GluR2 subunit, which is impermeable to Ca^{2+} and determines the critical biophysical properties of the receptor (Isaac et al. 2007; Hanley 2014). Thus, the change in AMPA receptor Ca^{2+} permeability shows significant influences on synaptic transmission and intracellular signaling events. In stroke model with middle cerebral artery occlusion, rats with rTMS stimulation over ipsilesional sensorimotor cortex exhibited obvious upregulation in post-synaptic density protein 95 (PSD 95), glutamate receptor 2/3 (mGlu 2/3R), and synapsin-1 (SYN) in the ipsilateral sensorimotor cortex (Gao et al. 2020).

The activation of GluN2A-containin NMDARs might contribute to neuronal survival, whereas activation of GluN2B-containing NMDARs can induce neuronal death in the early period of stroke (Ge et al. 2020). Owing to the ischemia-induced reduction of NMDARs, it is critical for neuroprotection to normalize the activities of NMDARs post-stroke (Liu et al. 2010). ITBS intervention can significantly improve the cognitive impairments caused by cerebral small vessel disease in stroke-prone renovascular hypertensive rats. The associated mechanisms were likely

related to the increased expression of NMDAR subunits NMDAR1, NMDAR2A and NMDAR2B, and AMPAR subunit GluR1, and p-CaMKIIα in the hippocampus. (Cai et al. 2020). The combination of brain stimulation (transcranial direct current stimulation and rTMS) and minocycline intervention also can increase neuroprotective effect by increasing neuronal and synaptic activity by activation of NMDAR (Alam et al. 2016). Conversely, blockade of NMDARs can weaken iTBS-reduced activation of inhibitory interneuron subtypes expressing GAD67 and PV (fast spiking vs. non-fast spiking subtypes) (Labedi et al. 2014). Thus, the effects of rTMS are deeply related to synaptic plasticity changes by increasing the expression of NMDARs.

Brain-derived neurotrophic factor (BDNF) also participated in mechanisms of rTMS-induced synaptic plasticity after ischemic stroke (Zhang et al. 2007; Cui et al. 2020). It is a neurotrophic factor and is necessary for learning and memory by supporting neuronal growth and driving AMPARs to synapses (Keifer 2022). BDNF can facilitate the regeneration of endothelial progenitor cells by modulating the complex changes in the microRNAs expression (He et al. 2018). A previous study also reported that BDNF exerts neuroprotection by modulating NMDAR/Ca^{2+}-dependent signaling (Lau et al. 2015). In ischemic rats induced by the two-vessel occlusion, rTMS can improve learning and memory function through facilitating BDNF expression. Subsequently, rTMS restored cholinergic system activity by increasing choline acetyltransferase and acetylcholinesterase activity, and enhancing the density of cholinergic neurons in the hippocampus of rats (Zhang et al. 2018). In the oxygen–glucose deprivation (OGD) model of primary neurons or the cerebral ischemic rat model, the expression of BDNF was upregulated in the cortex after rMS or pairing TMS intervention (Gao et al. 2020; Li et al. 2020). Furthermore, the increased methyl CpG binding protein 2 (MeCP2) phosphorylation can prompt the interaction between BDNF exon IV and receptor for activated C kinase 1 (RACK1), which might be the mechanism of TMS-induced synaptic plasticity (Li et al. 2020).

rTMS can induce the change of synaptic associated genes in an animal model with stroke. By bioinformatics analysis, the major functional category in the hippocampus of rats with rTMS was involved in chemical synaptic transmission regulation. Several differentially expressed genes (DEGs), such as Dlx6, Calb2, Zic1, Crhr2, and Gng4, were enhanced as verified by quantitative Real-Time PCR (qPCR) (Hong et al. 2021). In those associated genes, calretinin (Calb2) is associated with the formation of learning and memory by regulating long-term potentiation. Calb2 also plays an important role in cognitive function in mice with Alzheimer disease (Camp and Wijesinghe 2009; Coronas-Samano et al. 2016). However, the effect of the other genes in the

development of ischemic stroke remains to be explored. rTMS-induced change of synaptic associated genes might be associated with the activation of second messenger. A previous study has reported that rTMS can strongly activate the phosphorylation of ribosomal protein S6, which is a hallmark of activating AKT-mTOR pathway and immediate early gene expression (Pirbhoy et al. 2016). rTMS also strongly increased expression level of the immediate early genes Arc and c-fos in cortical neurons (Pirbhoy et al. 2016).

Those alterations of synaptic plasticity, such as the increased number and activity of synapses, contribute to the surviving brain regions undertaking the function of impaired brain tissues (Jones and Adkins 2015; Okabe et al. 2016). However, the effects of rTMS on network reorganization are still unclear. Taken together, rTMS can induce the beneficial changes in the structure, number, and function of the synapses and prompt the potentiation of excitatory synaptic transmission by modulating synaptic plasticity-associated proteins and genes, as shown in Fig. 1.

The Effect of rTMS on Neurogenesis

After ischemic stroke, endogenous neural stem cells (NSCs) often migrate to the damaged area and differentiate into astrocytes to the formation of glial scar instead of neurons (Faiz et al. 2015). In the subventricular zone (SVZ), 10 Hz rTMS over the ipsilateral M1 cortex significantly facilitated the proliferation of adult NSCs via mediating the miR-25/p57 pathway in the infarct cortex following cerebral ischemic injury (Guo et al. 2014). In a recent study, rTMS over the ipsilateral M1 cortex can facilitate the migration of NSCs and lower neuronal loss by increasing the expression of the stromal cell-derived factor-1α (SDF-1α)-1α/CXC chemokine receptor 4 (CXCR4) axis in peri-infarct cortical tissue of rats with ischemic stroke (Deng et al. 2021).

A previous study showed for the first time that the combination of rTMS over the ipsilateral hemisphere and human NSCs exerted effective effects on functional recovery by increasing neurogenesis and the expression of BDNF following ischemic stroke. They also found that rTMS can facilitate the neural differentiation of human embryonic stem cells (ESCs) in the forebrain (Peng et al. 2019). Additionally, LF-magnetic stimulation and iTBS can facilitate the generation of mature neurons from human-induced pluripotent stem cells (iPSCs). HF-magnetic stimulation can facilitate vesicular glutamate transporters 2 (Vglut2) transcription in iPSC-derived neurons (Liu et al. 2020), consisting with the effect of TMS in promoting neurogenesis.

In addition, rTMS over the ipsilateral hemisphere can regulate BDNF/tropomyosin-related kinase B (TrkB) pathway to facilitate neurogenesis in the ipsilateral hippocampus (Guo et al. 2017). Conventional 20 Hz rTMS or iTBS
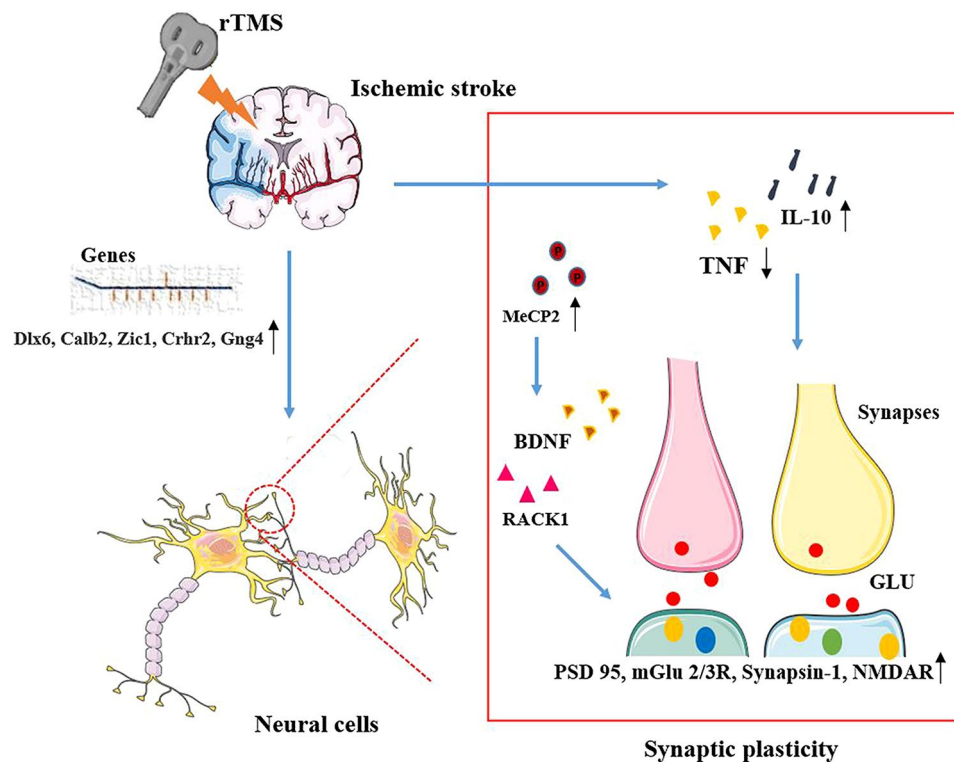
Fig. 1 Mechanisms of rTMS in synaptic plasticity after ischemic stroke. Several molecules play important roles in the modulation of synaptic plasticity. After ischemic stroke, rTMS can enhance the levels of synaptic plasticity-associated genes, such as Dlx6, Calb2, Zic1, Crhr2, and Gng4, and Grin3a; rTMS can also inhibit the overexpression of pro-inflammatory cytokines TNF, and facilitate the expression of anti-inflammatory cytokines IL-10 to improve the environment of synaptic growth; In addition, rTMS-induced MeCP2 phosphorylation facilitated the expression of BDNF and the interaction between BDNF exon IV and RACK1. Ultimately, those proteins and genes can improve the structure and function of synapses by up-regulating the levels of PSD 95, mGlu 2/3R, and synapsin-1. *rTMS* repetitive transcranial magnetic stimulation, *NMDAR N*-methyl-ᴅ-aspartic acid receptors, *BDNF* brain-derived neurotrophic factor, *PSD 95* post-synaptic density protein 95, *mGlu2/3R* glutamate receptor 2/3, *MeCP2* methyl CpG binding protein 2, *RACK* receptor for activated C kinase 1, *GLU* glutamate

over the ipsilateral M1 cortex significantly decreased the infarct area and improved neurological function. These beneficial effects might be related to facilitating neurogenesis as shown by the upregulation of Ki67/Nestin, Ki67/NeuN, and Ki67/DCX-positive cells in the striatum surrounding the infarct region and activating the BDNF/TrkB signaling pathway in the ipsilateral hemisphere excluding infarct area (Luo et al. 2017). BDNF/TrkB-specific inhibitor ANA12 can abolish the activation of BDNF/TrkB/AKT pathway and the proliferation of neural stem cells (NSCs) in the model of OGD plus reoxygenation (He et al. 2020). Importantly, rTMS also exerted a restorative effect by facilitating the proliferation and neuronal differentiation of NSCs, possibly through the MAPK signaling pathway in mice with intracerebral hemorrhage (ICH) (Cui et al. 2019). Newborn neurons after ischemic stroke can generate functional projections to the other brain regions, which might be important for motor functional recovery (Sun et al. 2012). However, a great deal of evidence remains to be explored in the future. Thus, neurogenesis

caused by rTMS exerted an important role in the restoration of neural network.

The Effect of rTMS on Neural Immune Response

There are several studies have shown the benefits of rTMS in improving the damage of ischemic stroke by regulating neural immune response. In the PT model, rTMS over the infarcted hemisphere can modulate complex cytokine response by decreasing peripheral immune cell infiltration in the peri-infarct area (Zong et al. 2020a, 2020b). There is a shift in astrocytic phenotypes from A1 to A2, and a switch in microglial M1/M2 phenotype activation after rTMS intervention (Zong et al. 2020a). In the vessel, the astrocytic A2 phenotypes significantly increased after the application of rTMS, which causes a reduction of excessive astrocyte-vasculature interactions in the peri-infarct zone. The associated mechanism was related to enhanced levels

of platelet-derived grow factor receptor beta (PDGFRβ) that mediated the interaction of A2 astrocytes and their neighbor vasculature (Zong et al. 2020b).

In a cell study, rTMS can effectively inhibit neurotoxic astrocytic polarization in the astrocytes culture medium after OGD/R injury. Specifically, the level of pro-inflammatory mediator TNF was downregulated and anti-inflammatory mediator IL-10 was upregulated after OGD injury (Hong et al. 2020). Calcitonin gene-related peptide (CGRP) is a neuropathic pain-related molecule and might be a potential mechanism of anti-inflammation of rTMS over trigeminal ganglion after focal ischemic stroke. rTMS can facilitate the secretion of CGRP by alleviating the levels of TNF and IL-1β, and reducing the number of activated microglia in the cerebral cortex. The inhibitor of CGRP can abolish rTMS-induced the reduction of infarct area and the increase of TNF and IL-1β (Wang et al. 2020).

In addition, rTMS also exerted the neuroprotective effect by regulating superoxide production, NADPH oxidase activity, and oxidative neuronal damage in the peri-infarct regions. After PT stroke, the levels of superoxide anion production and the activity of NADPH oxidase were significantly decreased on days 5 and 21. However, the level of mitochondrial manganese superoxide dismutase (MnSOD) was increased and the release of anti-inflammatory cytokines was reduced in peri-infarct areas after rTMS intervention (Zong et al. 2020a). Thus, rTMS can facilitate neural immune response by regulating A2 astrocyte, M2 microglia, and inhibiting oxidative stress in ischemic animals.

The Effect of rTMS on Blood–Brain Barrier Disruption (BBB) and Vascular Repair

rTMS can exert a great protective effect by promoting the restoration of the peri-infarct microvasculature and BBB following stroke, as shown in Fig. 2. In PT model, as shown by Zong et al. rTMS over the infarcted hemisphere can improve BBB function by mitigating BBB permeabilization and preserving important BBB components claudin-5, ZO-1, occludin, and caveolin-1 from PT-caused degradation in the peri-infarct zone. Furthermore, the damage to morphology, vascular structure, and perfusion was reversed by rTMS, contributing to the improvement of local tissue oxygenation. These results were accompanied by upregulation of regulatory factors and robust protection of critical vascular components. They also showed that rTMS can decrease the apoptosis of existing vascular and newborn endothelial cells in the peri-infarct zone, which plays a crucial role in a long-term angiogenesis effect (Zong et al. 2020b).

Moreover, angiogenesis-related factors TGFβ and vascular endothelial growth factor (VEGF) play important roles in vasculogenesis and angiogenesis (Patel-Hett and
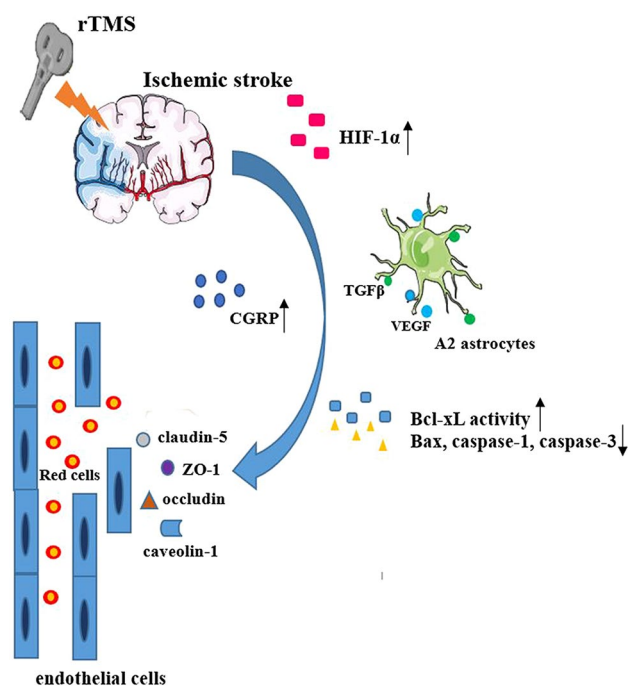
Fig. 2 Mechanisms of rTMS in BBB after ischemic stroke. rTMS can facilitate the ischemia-induced increase of HIF-1α and A1 shift to A2 in vessel-associated astrocytes. The increased HIF-1α can promote the release of angiogenesis-related factors TGFβ and VEGF in A2 astrocytes. In addition, TMS can also facilitate the secretion of CGRP, increase the activity of Bcl-xL, and decrease the activation of Bax, caspase-1, caspase-3. Ultimately, those molecules can improve BBB function by mitigating BBB permeabilization by enhancing the expression of claudin-5, ZO-1, occludin, and caveolin-1. *BBB* blood–brain barrier disruption, *HIF-1α* hypoxia-inducible factor-1α, *CGRP* calcitonin gene-related peptide, *VEGF* vascular endothelial growth factor

D'Amore 2011). There were obvious amplifications of TGFβ and VEGF in A2 astrocytes of the peri-infarct zone, indicating that A2 astrocytes might secrete cluster VEGF onto the vasculature. In addition, rTMS treatment markedly promoted PT-induced increase of hypoxia-inducible factor-1α (HIF-1α) which was reported to be upstream of VEGF (Zong et al. 2020b).

rTMS over the ipsilesional M1 cortex can improve cerebral blood flow (CBF), potentially by enhancing Bcl-xL activity and decreasing Bax, caspase-1, and caspase-3 activations in the striatum of animals with ischemic stroke (Caglayan et al. 2019). In addition, rTMS over trigeminal ganglion can also improve CBF in the middle cerebral artery (MCA) dominated area by promoting the secretion of calcitonin gene-related peptide (CGRP) in serum and cerebral cortex, which was reversed by CGRP8-37, an antagonist of CGRP (Wang et al. 2020). CGRP, as reported by a previous study, can decrease BBB disruption by improving ultrastructural damage in capillary endothelium cells of rats with ischemic stroke (Liu et al. 2011).

Thus, the associated mechanism of rTMS-induced BBB and CBF recovery is related to regulating HIF-1α signaling, and prompting A1 to shift to A2 in vessel-associated astrocytes, inhibiting apoptosis and increasing the secretion of CGRP in serum and cerebral cortex.

The Effect of rTMS on Neural Cell Death

Cell apoptosis is an important pathophysiology process of ischemic stroke and participated in the mechanisms of rTMS treating ischemic stroke. The pro-apoptotic protein, such as caspase-1, caspase-3, Bcl-2-associated protein X (Bax), and the anti-apoptotic protein, such as Bcl-2, and Bcl-xL, play key roles in regulating the progress of apoptosis (Khoshnam et al. 2017). The cleavage of caspase-3 can initiate apoptosis, but the anti-apoptotic proteins have special significance in that they can determine if the neural cells commit to apoptosis or abort the process (Elmore 2007). Previous studies indicated that rTMS over the ipsilesional hemisphere decreased infarct volume, and improved cognitive and motor function, which is related to the inhibition of apoptosis by increasing the Bcl-2 level and decreasing the caspase-3 and Bax level following ischemic stroke (Yoon et al. 2011; Guo et al. 2017; Caglayan et al. 2019). rTMS can also effectively inhibit the intrinsic mitochondrial membrane caspase-3/9 apoptotic pathway and preserve mitochondrial membrane integrity in the cortex surrounding the infarct region (Zong et al. 2020a). The percentage of TUNEL-positive cells was significantly decreased after rTMS intervention in the ipsilateral hippocampus or cortex after stroke (Guo et al. 2017; Zong et al. 2020a). In addition, TMS combined with electroacupuncture can improve neurological function, which was associated with the upregulation of Bcl-2 mRNA level and downregulation of caspase-3 expression in infarcted areas (Li et al. 2012).

In addition, iTBS could alleviate ischemic injury-induced locomotor dysfunction and neuronal pyroptosis by modulating innate immune and inflammatory responses. There were observed significant decreases in IL-1β, IL-17A, TNF, IFN-γ, an increase in IL-10, and reductions in neuronal pyroptosis-associated proteins, such as Caspase-1, IL-1β, IL-18, ASC, NLRP1, and cleaved Caspase-1 cleaves Gasdermin D (GSDMD), in the peri-ischemic area rather than in the border of ischemic core. Moreover, iTBS shifted the balance of microglial M1/M2 phenotype by suppressing pro-inflammatory M1 activation and elevating the anti-inflammatory M2 activation in the peri-ischemic area via suppressing TLR4/NFκB/NLRP3 signaling pathway (Luo et al. 2022). Taken together, the rTMS can improve cognitive and motor function by suppressing apoptosis and pyroptosis.

Future Directions for Animal rTMS

The Effect of rTMS in Glial Cells

Glial cells play a critical role in synaptic remodeling owing to they are associated with synaptic plasticity and neuronal connectivity. Neuronal circuits undergo ongoing structural alteration by synaptic interconnecting in response to experience. Synapses are constantly formed and eliminated, which are associated with astrocyte and microglial interaction and regulation. After ischemic stroke, synapse remodeling is crucial to change the structure of neuronal circuits to produce functional compensation (Tennant et al. 2017; Wahl et al. 2017). Exploring remodeling processes is essential for understanding how experiences modulated plasticity and promoting functional rehabilitation. According to a report by Phi T. Nguyen et al., the molecular interaction between microglia and neurons can drive experience-dependent synapse remodeling (Nguyen et al. 2020). Thus, we speculated that rTMS might remodel impaired synapses by regulating molecular interaction between microglia and neurons. Therefore, extending experiments to explore glial cells such as astrocytes and microglia may progress our cognition of the synaptic plasticity and find new therapeutic targets for rTMS.

The Exploration of Dual-Site Stimulation

There have been many dual-site stimulations in the post-stroke, especially in the ipsilesional and contralesional hemispheres. However, the brain stimulation combined with the peripheral nerve stimulation might exert benefits for post-stroke dysfunction by prompting the synaptic connection between the center neural system and peripheral nerve. Paired associative stimulation (PAS) is a protocol to produce synaptic plasticity non-invasively in healthy individuals and patients with stroke or other disorders (Dixon et al. 2016; Kumar et al. 2017; Palmer et al. 2018). It aims to synchronize the activity of presynaptic neurons to elicit spike-timing-dependent plasticity (Feldman 2012). The combination of non-invasive electrical stimulation over the spinal cord or peripheral nerves and TMS over the motor cortex was the most common PAS for motor function recovery. However, the associated basic mechanisms remain unclear. In the future, basic researches are essential to explore the associated mechanism of dual-site stimulation targeting synaptic plasticity. Those mechanisms can contribute to progressing our understanding of changes in the synaptic connection between the center neural system and peripheral nerve.

Others

In addition, several key issues involving the role of TMS in the treatment of stroke still require to be explored. In this review, the majority of studies were related to the application of HF TMS over the ipsilesional hemisphere despite no obvious difference between the effect of HF and LF TMS. The cerebellum also participates in the regulation of cortical excitability, and rTMS or TMS over the cerebellum is also a treatment option for stroke. In a randomized clinical trial, cerebellar iTBS showed an enhancement of gait and balance recovery and an increase in neural activity over the posterior parietal cortex by affecting cerebello-cortical plasticity in patients with hemiparetic stroke (Koch et al. 2019). However, the mechanisms in molecular biology remain to need to be explored in animal experiments.

Single-pulse TMS is often used as a sensitive strategy to quantitatively assess the functional state of the motor system (Escudero et al. 1998; Bolay et al. 2000; Lyseniuk et al. 2014). It is always applied to the cortex but not the deep brain areas. A recent study showed that deep magnetic induction tomography (MIT) combined with improved TMS coils enables the detection of hemorrhagic stroke in humans, providing a crucial base for a deeper research of deep strokes (Lv and Luo 2021). Thereby, the application of TMS to deep stroke detection needs to be studied in the future. Moreover, the duration, initiation time, intensity, and frequency of stimulation also need to be explored in the future.

Conclusion

In this review, we investigate the mechanisms of TMS for treating ischemic stroke. Those mechanisms are essential to progress our understanding of rTMS-induced improvement of the dysfunction after ischemic stroke. rTMS can contribute to the potentiation of excitatory synaptic transmission by modulating synaptic plasticity-associated proteins and genes. In addition, rTMS can significantly inhibit neural cell death, regulate immune response, promote neurogenesis and improve BBB and vascular repair. In the future, more molecular mechanisms will be explored to understand the scope and capacity of rTMS for treating different neurological diseases.

Data Availability Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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