Molecular Neurobiology
https://doi.org/10.1007/s12035-020-02021-1

REVIEWS

A Review of Exercise-Induced Neuroplasticity in Ischemic Stroke: Pathology and Mechanisms

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Received: 24 May 2020 / Accepted: 8 July 2020

Abstract
After ischemic stroke, survivors experience motor dysfunction and deterioration of memory and cognition. These symptoms are associated with the disruption of normal neuronal function, i.e., the secretion of neurotrophic factors, interhemispheric connections, and synaptic activity, and hence the disruption of the normal neural circuit. Exercise is considered an effective and feasible rehabilitation strategy for improving cognitive and motor recovery following ischemic stroke through the facilitation of neuroplasticity. In this review, our aim was to discuss the mechanisms by which exercise-induced neuroplasticity improves motor function and cognitive ability after ischemic stroke. The associated mechanisms include increases in neurotrophins, improvements in synaptic structure and function, the enhancement of interhemispheric connections, the promotion of neural regeneration, the acceleration of neural function reorganization, and the facilitation of compensation beyond the infarcted tissue. We also discuss some common exercise strategies and a novel exercise therapy, robot-assisted movement, which might be widely applied in the clinic to help stroke patients in the future.

Keywords Ischemic stroke · Exercise · Neuroplasticity · Neurotrophins · Regeneration · AMPA receptors

Introduction

Stroke is a cerebrovascular disease characterized by high morbidity, mortality, and disability. The occurrence rate of acute first-ever ischemic stroke is higher than that of acute first-ever hemorrhagic stroke in terms of the Global Burden of Disease (GBD) 2015 study [1]. In 5-year post-stroke survivors, two-thirds showed good functional outcome in neurologic deficit and disability, 20% underwent a second stroke, 22.5% showed dementia symptoms, 29.6% showed depression, and approximately 15% were institutionalized [2]. The symptoms after ischemic stroke are associated with the disruption of normal neuronal function, i.e., interhemispheric connections and synaptic activity, due to neuronal death in the ischemic core and hence the disruption of the normal neural circuit [3–5]. The recovery processes induced by various therapies often involve spared axonal sprouts that contribute to establishing new circuits by innervating denervated target regions [6–8]. That is, functional recovery after ischemic stroke is related to neuroplasticity.

Neuroplasticity is defined as structural and functional changes in the brain that enable adaptation to learning, memory, the environment, and rehabilitation following brain damage. It is a dynamic process involving alterations in the number of brain nuclei and structures, numerous functions, and various interactions [9–11]. Although there are spontaneous remodeling changes that occur after brain injury following ischemic stroke, these changes are not sufficient to produce obvious functional recovery [7]. In the normal and injured brain, rehabilitation can promote dynamic processes in the nervous system to allow adaptation to different experiences [12, 13]. Thus, based on neuroplasticity research, it is very important to find an effective method for the rehabilitation and treatment of brain injury following ischemic stroke.

Exercise is considered an effective and feasible rehabilitation strategy for improving cognitive and motor functional recovery through the facilitation of neuroplasticity such as through increases in neuronal activity and the potentiation of postsynaptic excitation, as well as enhancements in dendritic spine formation and axonal myelination following ischemic stroke [14]. Several clinical and animal studies have shown

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Published online: 20 July 2020

significant functional improvement following stroke when rehabilitation training is performed [15–18]. In an exploratory study on chronic stroke, physical training exerted significant effects on mobility, and some patients showed obvious cognition improvements, which were paralleled by cerebral activity changes that probably reflected neuronal plasticity [19]. The expression of neuroplasticity-relevant genes, such as protein kinase C (PKC) ζ, *N*-methyl-D-aspartate (NMDA) 2A receptor, neurotrophic tyrosine kinase receptor 2 (NTRK 2), or microtubule-associated protein (MAP) 1b, was significantly changed in rats exposed to both forced arm use and voluntary exercise after photothrombotic stroke to improve functional recovery [20]. Therefore, the aim of this review is to discuss the mechanisms by which neuroplasticity induced by exercise training improves motor function and cognitive ability after ischemic stroke.

Nerve Impairments in Stroke Pathophysiology

Cerebral ischemic stroke is often triggered by embolic or thrombotic arterial obstruction causing decreased cerebral blood flow. Thus, a gradient of decreased blood flow emerges, causing severe tissue injury and blood flow reduction and resulting in a surrounding penumbra in which degenerative reactions and blood flow reduction are less extreme [21]. Ischemic stroke causes two primary pathological processes, namely, oxygen loss and an interruption in glucose supply to targeted brain areas, triggering a complex molecular cascade consisting of blood–brain barrier disruption [22], reactive oxygen species (ROS) production [23], excitotoxicity [24], cell membrane depolarization [25], slowed cellular energy metabolism [26], inflammatory responses by activated microglia [27], and apoptotic cell death [28].

Stroke can also result in bioenergetic collapse and mitochondrial dysfunction in neural cells. Bioenergetic collapse and mitochondrial dysfunction are related to reduced adenosine triphosphate levels and dysfunction of the sodium-potassium pump, such as dysfunction of sodium-potassium adenosine triphosphatase (Na^+/K^+ATPase) and opening of calcium (Ca^{2+}) channels, further triggering more severe pathophysiological disorders, an increase in the depolarization of the neuronal membrane potential, generation of oxygen free radicals, excitatory neurotoxicity, etc. [29–32]. Intracellular Ca^{2+} homeostasis plays a key role in controlling neuronal activity, including synaptic plasticity, neurotransmitter release, and neuronal death [33]. Ca^{2+} flux triggers synaptic vesicle endocytosis, which regulates neurotransmitter release to maintain synaptic transmission [34, 35]. Hence, the opening of Ca^{2+} channels can enhance Ca^{2+} transfer from the endoplasmic reticulum (ER) to mitochondria and further cause excitatory neurotoxicity and neuronal death in ischemia [36, 37]. These impairments following stroke can cause disruption of neuronal function that is associated with some forms of motor, sensory, or cognitive impairments that occur in the majority of survivors after stroke.

During the post-stroke recovery stage, the functional brain networks spontaneously experience rewiring and reorganization of surviving neural networks due to structural lesions that tend to appear contralateral as well as ipsilateral to the damage accompanied by functional recovery [38–41]. These spontaneous neuroplasticity changes might be associated with pathophysiological mechanisms, such as the release of neurotropic factors [42]; regulation of anti-inflammatory cytokines [43]; nerve regeneration [44]; structural remodeling at the synaptic, axonal, and dendritic levels [45]; and activation, migration, and differentiation of endogenous neural stem cells [46]. Spontaneous recovery is also related to associated gene changes in the motor cortices of stroke mice, such as a reduction in dopamine receptor D2 (Drd2), adenosine receptor A2A (Adora2a), and phosphodiesterase 10A (Pde10a) expression in the contralesional cortex [47]. Understanding the mechanisms of neural impairment and remodeling will allow the exploration of the relationship between neuroplasticity and exercise rehabilitation.

The Mechanisms by Which Exercise-Dependent Plasticity Improves Functional Recovery

Exercise Improves Dendrites and Axons

Dendrites and axons are important components of neurons and play a crucial role in exercise-dependent neuroplasticity. The number of dendritic arborizations in the injured cortical area of rats is significantly lower after ischemic stroke. Constraint-induced movement therapy (CIMT) can effectively increase dendritic arborizations, particularly in layer III pyramidal neurons, and reestablish axonal connections between the hemispheres [48]. Reach training preceded by running slightly increases MAP2 expression in the contralateral motor cortex compared with the ipsilateral cingulate cortex and contralateral sensory cortex, indicating more dendritic branching in the motor cortex of rats [49]. Brain-derived neurotrophic factor (BDNF) is formed by the posttranslational modification of a glycosylated precursor protein, precursor BDNF (proBDNF), into the mature form, mature BDNF (mBDNF) [50]. It has been reported that aerobic exercise for 4 weeks may elevate the ratio of mBDNF/proBDNF in the ischemic hippocampus of rats [51]. A balance between mBDNF and proBDNF plays an important role in dendritic spine plasticity due to the opposing effects of mBDNF and proBDNF on neural plasticity [52]. Dendritic complexity and the expression of postsynaptic density 95 (PSD-95) and BDNF are

significantly enhanced in the bilateral hippocampi of rat submitted low-intensity exercise compared with sedentary rats, and spatial memory performance is obviously improved. High-intensity exercise does not notably improve spatial memory performance or synaptic plasticity [53].

Axonal plasticity is enhanced after a combination treatment of task-specific training and infusion of 5-aza-2′-deoxycytidine (an inhibitor of DNA methylation), which might be a promising approach for promoting functional recovery in rats with photothrombotic ischemia in the chronic stage of stroke [54]. Exercise training facilitates axonal recovery related to the downregulation of Nogo-A/Nogo66 receptor–1 (NgR1)/Rho A in the ischemic area of hypertensive stroke rats [55]. CIMT facilitates axonal growth and improves synaptic plasticity at least partially by overcoming intrinsic axonal growth-inhibitory signals to improve behavioral deficits. The expression levels of Rho A/Rho-associated kinase and Nogo-A/Nogo receptor are significantly downregulated in the denervated cervical spinal cord of rats [56]. Growth-associated protein 43 (GAP-43) is observed in the axonal extensions of the majority of neurons during neural development [57]. Exercise may increase the expression of GAP-43 and PKC, which is related to exercise-induced paralysis recovery. The interaction between GAP-43 and PKC is associated with the remodeling of cortical connections and neuronal plasticity in rat with cerebral infarction [58, 59].

In summary, these results are sufficient to indicate that plastic alterations occur in dendrites and axons. Increased dendritic arborization and axonal growth might contribute to shaping new synaptic connections, thus promoting reorganization of neural function.

Exercise Facilitates Synaptic Plasticity

Synaptic plasticity is important for neural recovery after brain injury. Cerebral ischemia may result in impairment of synaptic structure involved in the development of functional dysfunction [60]. It has been reported that synapses in the peri-infarct area exhibit comparatively intact presynaptic and postsynaptic membranes and increased synaptic vesicles at the presynaptic membranes [61]. To date, there is much evidence showing that the recovery of neurological function underlies synaptic repair after ischemic stroke [60, 62, 63].

There is an important concept in neurobiology that "neurons fire together, wire together," which means that the activation of synapses subserves the formation and maintenance of synapses [64]. Rehabilitative training may enhance the stability of new synapses formed during the initial weeks in rats following brain infarct. The magnitude of stability is related to improvements in skilled motor performance [65]. There are obvious but transient enhancements in the synapse-to-neuron ratio and axospinous synapse density in rats exposed to a spatial learning task compared with untrained age-matched rats, and these enhancements are accompanied by transient reductions in both the postsynaptic density area and mean synaptic height. Changes in the dentate gyrus are possibly associated with memory formation [66].

Motor training, especially skill training related to coordination and balance, contributes to uniquely lateralized synaptogenesis in the thalamus [67]. Willed-movement training involves training animals to climb the walls or ladder of a device to reach water and food. It is more beneficial than swimming or environmental modification in increasing protein interacting with C kinase 1 protein (PICK)–regulated synaptic plasticity in the region surrounding the ischemic area in rats [68]. Here, we discussed some factors involved in exercise-dependent synaptic plasticity to further understand the mechanisms of functional improvement following stroke.

A-Amino-3-Hydroxyl-5-Methyl-4-Isoxazole-Propionate (AMPA) Receptors

AMPA receptors largely regulate excitatory neurotransmission and activity-dependent plasticity [69]. The mRNA levels of GluA1 and GluA4 are markedly increased after willed-movement intervention in rats in the subacute stage of ischemic stroke, improving synaptic transmission and brain plasticity [70]. In our previous study, modified CIMT was shown to exert a positive effect in ischemic rats by facilitating the expression of GluA2/3 and postsynaptic density 95 (PSD-95), as measured by western blotting and transmission electron microscopy, and by regulating neurotransmitter receptor genes, specifically by increasing glutamate ionotropic receptor AMPA type subunit 3 (Gria3) expression [71].

NMDA Receptors

NMDA receptors are ionotropic glutamate–gated receptors that are composed of the NMDA receptor subunit type (GluN)1, GluN2, and GluN3 subunits. The composition of NMDA receptors is strictly modulated by activity-dependent synaptic plasticity during development. Over the past few years, pre-ischemic treadmill training has been proven to inhibit the overexpression of GluN2B and the mRNA expression of metabotropic glutamate receptor 5 (mGluR5) and reduce brain damage, possibly through the phosphatidylinositol 3-kinase (PI3K)/Akt-glutamate transporter-1(GLT-1)-glutamate and PKC-α-GLT-1-glutamate pathways in post-ischemic rats [72]. Phospho-GluN2B expression in the hippocampus of rats is also markedly decreased, and this change might partially contribute to physical exercise-induced neuroprotective effects [73]. Recently, by performing western blotting and immunohistochemistry after training, Luo et al. measured the expression of GluN2A and GluN2B proteins and found increased levels of GluN2B and decreased levels of GluN2A proteins in the hippocampus of rats after ischemic

stroke [74]. Treatment with bis(propyl)-cognitin, an antagonist of NMDA receptors, after stroke can potentiate the rehabilitative effects of treadmill exercise, probably by increasing vascular endothelial growth factor (VEGF) expression in the brain, further demonstrating the key role of NMDA receptors in exercise-dependent synaptic plasticity [75].

Neurotrophins

There are some common neurotrophins, including BDNF, GAP-43, and insulin-like growth factor (IGF-1). Increases in neurotrophins induced by exercise training play important roles in promoting synaptic plasticity, as shown below.

Exercise improves motor and cognitive impairment in ischemic mice following stroke by promoting neurogenesis, angiogenesis, and synaptic plasticity via the caveolin-1/VEGF signaling pathway, which is related to BDNF [76]. Exercise-induced paralysis recovery of brain ischemic rats may be related to the upregulation of both GAP-43 phosphorylated at serine 41 (pSer41-GAP-43) and GAP-43. The possible mechanisms, which include neurite formation, synaptic connections, and remodeling, might be related to the interaction between GAP-43 and calmodulin, PKC, and nerve growth factor (NGF) [59]. Moreover, the combination of physical exercise and Buyang Huanwu may improve neural behavioral deficits, maintain the synaptic ultrastructure, and significantly increase the levels of synaptophysin (SYN), MAP-2, and GAP-43 in rats after cerebral ischemia [77]. Ploughman et al. indicate that relatively modest exercise can upregulate the expression of proteins associated with synaptic plasticity, such as IGF-1, synapsin-I, and BDNF, in brain regions, possibly contributing to motor in rats following ischemic stroke [78]. In a clinical study, aerobic exercise with cognitive training, which might be involved in the upregulation of serum IGF-1 levels, robustly improves cognition in patients > 6 months post-stroke. Therefore, IGF-1 might participate in behaviorally induced plasticity [79].

In addition to the abovementioned factors, there are also many other factors that participate in exercise-induced neuroplasticity. Physical exercise may improve cognitive performance in patients after stroke through several neurobiological mechanisms that are related to growth factors, such as VEGF [80], which may be mediated by caveolin-1 to promote synaptic and dendritic plasticity [81].

Taken together, regulating BDNF, GAP-43, IGF-1, and other growth factors caused by exercise training plays important roles in promoting synaptic plasticity. Thus, it is essential to discuss the important role of neurotrophins in exercise-dependent neuroplasticity.

Other Synapse-Related Proteins

The expression of synaptic-related proteins is positively correlated with synaptic plasticity. Exercise training has been proven to promote synaptic plasticity by increasing the expression of synaptic-related proteins in cerebral ischemic rats, including SYN [82], synapsin-I [83], PSD-95 [53, 84], vesicular glutamate transporter (vGlut)1, vGlut2, and vesicular GABA amino acid transporter (vGAT) [85]. Immunohistochemistry and western blotting showed that CIMT significantly increases the expression of vGlut1, PSD-95, GAP-43, and SYN in the denervated cervical spinal cord in rats subjected to stroke [56]. In the entorhinal cortices of rats subjected to ischemic stroke, the levels of SYN and PSD-95 are increased, as measured by western blotting [84]. SYN and synapsin-I are associated with the packaging, storage, and release of synaptic vesicles [83]. Rats that undergo exercise training exhibit a significant increase in SYN expression in the subcortical areas of the ipsilateral hemisphere, including the dentate gyrus, thalamus, and hippocampus [82], which might be involved in the regulation of PICK1 [68]. The number of SYN-positive cells is also notably increased, promoting synaptic plasticity in cerebral ischemia rats [61]. These proteins can benefit axonal growth and the activity of synaptic vesicles, resulting in synaptic activity and synaptic structure development.

In summary, regulation of AMPA receptors, NMDA receptors, neurotrophins, and other synapse-related proteins plays important roles in exercise training–dependent synapse plasticity by promoting synaptic structure, synaptic activity, and remodeling.

Exercise Improves Interhemispheric Connections

Animal Experiments

A severe loss of interhemispheric connectivity related to corresponding behavioral deficits and partial recovery during the chronic phase following stroke in mouse has been observed through widefield calcium imaging [86]. Contralateral tissues show increased interhemispheric inhibition compared with ipsi-infarct tissues following focal ischemic stroke in the forelimb motor cortices of mice [87]. Combining robotic rehabilitation and inactivation of the contralateral hemisphere may facilitate general motor recovery and fine motor function accompanied by normalizing transcallosal inhibition in post-stroke mice [87].

Clinical Studies

Interhemispheric motor connections play an important role in motor function following stroke and differ depending on the extent of motor impairment. Fractional anisotropy (FA) in the corpus callosum is obviously downregulated and positively correlated with motor function in patients with relatively mild motor deficits, while in patients with relatively severe motor deficits, motor function is correlated with FA in the corticospinal tract (CST) [88]. By using diffusion tensor imaging (DTI), Carter AR et al. showed that the extent of CST

damage was negatively correlated with interhemispheric connectivity, particularly the connectivity between the bilateral central sulci in 23 recruited stroke patients [89]. Hence, interhemispheric connectivity is related to the integrity of the corpus callosum and CST after stroke. Hence, inhibiting contralateral brain tissue might be a beneficial treatment for improving interhemispheric balance after stroke.

Mildly impaired patients showed improvements in the function of the affected proximal upper extremity related to suppression of the contralesional primary motor cortex (M1), but suppression of the contralesional M1 worsens paretic upper limb control in moderate to severely impaired patients. The effects of inhibiting the contralesional M1 depend on the integrity of the white-matter tracts that innervate the paretic upper limb from the ipsi-infarcted hemisphere following stroke [90]. In stroke patients, performing a unilateral voluntary hand-grasping task can increase ipsi-lesional M1 activation [91], and early intensive upper limb training can increase activation in the ipsi-lesional supplementary motor areas and anterior cingulate cortex, and reduce the activation of the contralesional cerebellum [92]. Importantly, excitatory connectivity from the ipsi-lesional to the contralesional M1 is enhanced by a unilateral voluntary hand-grasping task [91].

In summary, animal experiments and clinical studies have shown that exercise training can promote interhemispheric connectivity by increasing activation in ipsi-lesional cerebral regions, enhancing excitatory connectivity from the ipsi-lesional to the contralesional M1, and reducing transcallosal inhibition induced by stroke to facilitate motor function recovery.

Exercise Promotes Neuronal Regeneration

Newborn striatal neurons appear after ischemic stroke and can generate functional projections to the substantia nigra, which might be important for motor functional recovery [44]. Exercise training may significantly facilitate the regeneration capacity of newborn projection neurons in the ischemic brains of rats to improve motor function [93]. CIMT-induced recovery is involved in promoting axonal remodeling, survival, and the regeneration of corticospinal neurons to enhance ipsi-lesional corticospinal projections [94]. Interestingly, exercise training may also improve the regeneration of the contralesional pyramidal tract following ischemic stroke in rats [95]. Willed-movement therapy increases the expression levels of GAP-43 and neurotrophin 3 (NT-3), which is likely involved in nerve repair and regeneration in the ischemic brain in rats [96]. Specific combinations of growth factors may activate endogenous adult neural stem cells to encourage functional recovery and cortical tissue regrowth following stroke [97]. The combination of physical exercise and cognitive stimulation has more beneficial effects in increasing adult neurogenesis than either experimental intervention alone [80]. In addition, the enhancement of angiogenesis induced by exercise following ischemic stroke might be associated with the expression of metalloproteinase membrane type 1-metalloprotease (MT1-MMP) in cerebral microvessels surrounding the infarct region in rats [98]. Long-term exercise for 4 weeks facilitates neuroblast differentiation and cell proliferation in a time-dependent manner [99]. The neuronal cell proliferation induced by exercise has been proven to be involved in increasing myelin basic protein (MBP), PSD-95, SYN, NeuN, Nestin, B cell lymphoma-2 (Bcl-2), and Ki67 expression and decreasing SMI 32 (a marker of abnormally dephosphorylated neurofilament protein) expression in the entorhinal cortex [84]. Newly generated mature cells are observed in the granule cell layer of the dentate gyrus and might be related to improvements in memory deficits induced by long-term exercise [99]. However, early exercise training might be harmful to neural regeneration in the subventricular zone (SVZ) following the first week after stroke [100]. Exercise pretreatment for 3 weeks also exerts neuroprotective effects by decreasing the infarct area, neuronal apoptosis, and oxidative stress; improving motor function; promoting astrocyte proliferation; and increasing angiogenesis after ischemic stroke [101].

In summary, these results suggest that exercise can promote axonal regeneration and angiogenesis, increase the number of newborn neurons, and facilitate the projections from these newborn neurons.

Exercise Promotes Functional Reorganization of the Brain

Microstimulation and functional mapping studies have shown that recovery from stroke damage can lead to surviving brain areas undertaking the functional roles of impaired brain tissues [102]. After stroke, neuronal reorganization in the peri-infarct cortex plays a role in improving motor function [103], which is initiated through cellular reactions to degeneration [104]. As neurons in the ischemic region are subjected to death, their axons and synapses degenerate widely in brain regions, facilitating the generation of new connections among surviving neurons by instigating regenerative responses. The new connectivity that emerges from this process has tremendous variable potential in pattern and functional benefit [104].

Behavioral experiences following stroke potently promote neural reorganization by influencing the activity of regenerated circuits, as reviewed below. Skilled forelimb reaching training promotes the projection of neurons to the upper cervical cord, which provide new connections to the denervated forelimb area in the spinal cord, and these new connections contribute to motor map reorganization and exercise-induced task-specific recovery in the secondary motor area [105]. Use-dependent plasticity caused by repetitive motor training combined with brain stimulation may be associated with the

reorganization of task-specific multiregional brains. During trained extensor movements, brain activity in some regions, such as the contralesional premotor cortex, the contralesional cingulate motor cortex, and the ipsi-lesional sensorimotor cortex, is significantly reduced, and this is related to functional improvements in the affected hands [106]. Monkeys subjected to subthreshold electrical stimulation plus rehabilitative training show obvious improvements in motor performance (efficiency, speed, and success) that may persist for several months. Large-scale emergence of new hand representations in the peri-ischemic motor cortex is observed by cortical mapping [107].

Aging might be a factor influencing exercise-induce functional reorganization after ischemic stroke. After ischemic stroke, aged mice exhibit markedly larger infarct volumes than young mice. Task-specific rehabilitation training may improve motor function in both age groups. However, expansion of the rostral forelimb area is found in young mice, indicating that reorganization of the motor cortex might be limited by either the extent of brain injury or aging [108]. Hence, aged survivors or patients with worse brain injury could receive combined therapy instead of exercise training alone for a better therapeutic effect.

In summary, exercise-mediated post-stroke recovery can contribute to surviving brain areas undertaking the functional roles of impaired brain tissues by increasing axonal regeneration and the activation of new connections between surviving neurons. Moreover, the reorganization of cerebral function is also associated with the number of newborn neurons and increased dendritic arborization and axonal growth. It is quite possible that effects that result from exercise training are accompanied by alterations in axonal projections and the formation of new neural circuits from the same regions to other regions.

Excise Facilitates Neural Compensation Beyond Infarcted Tissue

Animal Experiments

The compensation of contralesional region exerted an important role and has been clarified in the ischemic rats. In our previous study, CIMT was shown to recruit more neuronal cells to the innervated network of the affected forelimb in the contralesional region than in the ipsi-lesional red nucleus and motor cortex [109]; CIMT also enhances the synapse number in the contralesional cortex [109] and increases glucose metabolism in the contralateral hemisphere, including the cortex insular and acbcore shell [110]. Recently, Gao et al. found that modified CIMT can effectively decrease glutamate content in the contralateral hippocampus, increase AMPA receptor protein, and regulate neurotransmitter receptor–related genes in the bilateral hippocampus [71]. Together, these results suggest that CIMT is an effective strategy for facilitating neural function compensation. After brain injury, CIMT, which results in reliance on the paretic limb, can enhance the capacity of the peri-infarct cortex, which benefits paretic forelimb function. Such compensation might tend to develop quickly and is a beneficial strategy for improving deficits.

Although the compensation of contralesional region has been proven, the compensation of the contralesional CST remains a controversial issue. Zhao et al. demonstrated that CIMT markedly enhances the number and length of midline crossings of contralateral corticospinal axons to the denervated cervical spinal cord in rats subjected to stroke [56]. However, our previous study found that CIMT can contribute to functional recovery after ischemic stroke by facilitating the remodeling of the ipsi-lesional CST, as assessed by DTI, and that this might be related to a decrease in the ratio of p-c-Jun N-terminal kinase (JNK)/JNK; however, the contralesional CST does not exhibit obvious remodeling [111]. The reason for the inconsistent results may be that the experimental animals had different degrees of brain damage.

Furthermore, the extrapyramidal system also exhibits significant functional compensation after stroke. Ishida et al. showed that individual corticobrainstem pathways exert a dynamic compensatory action for functional recovery through rehabilitative training following capsular stroke. The corticorubral tract is associated with intensive rehabilitation-induced recovery of forelimb function during the early phase following internal capsule hemorrhage, but the corticoreticular tract is related to rehabilitation-induced recovery when the function of the corticorubral tract is impaired [112]. At the level of cervical enlargement and the red nucleus, contralesional corticofugal tract axons exhibit increased plasticity in post-ischemic rats subjected to skilled reaching training and forced running wheel exercise. Rat subjected to skilled reaching training exhibit more contralateral corticorubral tract remodeling at the red nucleus level than rats subjected to forced running wheel exercise [113].

Clinical Studies

The compensation of contralesional region and extrapyramidal system also was indicated in post-stroke patients in clinical studies. As demonstrated by DTI, patients show progressive decreases in FA in the CST surrounding the ischemic lesion and progressive increases in FA increases in contralesional brain regions, such as the medial frontal gyrus, and thalamocortical connections that project to the premotor areas, primary motor cortex, and somatosensory cortices 4 and 12 weeks after acute subcortical infarct. The remodeling of contralesional brain regions is positively correlated with Fugl-Meyer scores and can prompt early motor recovery [38]. In post-stroke patients with severe CST injury, the bilateral rubrospinal tract may exhibit changes in FA and radial diffusivity (RD), indicating the important role of the rubrospinal tract in the recovery of hand function as shown by DTI [114].

In summary, exercise-mediated recovery of post-stroke damage can contribute to the functional compensation of surviving brain areas involved in limb function. The possible mechanisms include enhanced activity and axonal growth of the pyramidal and extrapyramidal systems in the ipsi-lesional and contralesional hemispheres. However, the role of the healthy hemisphere in post-stroke recovery is still controversial. As noted above, contralesional brain tissue is likely to be a main source of new neural connections in denervated regions after larger infarcts. Behavioral experience may be the biggest driver of these new connections to subserve functional improvements in the paretic forelimb.

Exercise Improves Motor and Cognitive Function

Current Exercise Strategies

Common exercise strategies include running exercise, skilled reaching training, voluntary exercise, and forced exercise. There are also many exercise strategies that can provide beneficial environment and/or effect in recovery of motor function in post-stroke patients.

Running Exercise and Skilled Reaching Training

Running exercise may improve learning and attention during the early phase of stroke rehabilitation by enhancing neurotrophic factors and other modulators related to synaptic plasticity [49]. However, it has a negative effect on neurogenesis in the post-ischemic hippocampus, as assessed by bromodeoxyuridine (BrdU) staining. The number of BrdU-labeled cells is enhanced in the granule cell layer (GCL) and subgranular zone (SGZ) in response to ischemic stroke but is decreased 14 days after ischemia in response to running exercise [115]; this is opposite of the increased neurogenesis induced by running exercise in the normal hippocampus [116].

The levels of neurotrophic factors may be increase in rats undergoing treadmill or skilled reach training. There are no obvious differences in the levels of NGF and BDNF between animals subjected to the two forms of exercise [117]. Skilled reaching training has greater effects in promoting motor recovery and axonal plasticity in the corticorubral tract after cerebral ischemia than forced running wheel exercise [113]. Reach training combined with running may significantly improve skilled reaching ability, but there is no improvement in postural support or gait in rats after ischemic stroke [49]. Skilled reaching training is likely more beneficial for fine exercise ability.

Forced Exercise and Voluntary Exercise

Aerobic exercise, particularly forced exercise, should be regarded as an effective strategy for accelerating the recovery of motor function after stroke, as Linder et al. proved that forced exercise before upper extremity repetitive task practice results in a greater acquisition than voluntary or stroke-associated training [118]. Early moderate forced exercise for 4 weeks beginning 24–48 h post-stroke has beneficial effects by alleviating lesion volume and inhibiting inflammation and oxidative damage in perilesional tissue [119]. CIMT, a common type of forced exercise in the clinic, rescues deficits in skilled movements following ischemic stroke and facilitates the recovery of fine movement [48]. A meta-analysis showed that low-intensity CIMT might have more beneficial effects than high-intensity CIMT in patients in the acute or subacute stage of stroke [120]. However, compared with forced exercise, voluntary exercise might significantly improve cognitive function. Both types of exercise may increase PSD-95, MAP-2, synapsin I, and Tau levels in the hippocampus, as determined by western blotting and immunohistochemistry. There are no significant differences in the reduction in neuronal and dendritic loss induced by two-pattern exercise, as assessed by Nissl staining [118].

Exercise Strategies in Clinic

There are various exercise rehabilitation procedures that have been performed in the clinic. Patients with residual hemiparesis underwent a 3-week balance training (Wii Fit for 60 min/day, 3 times/week), which promoted functional recovery by influencing neural plasticity possibly through an increase in corticomotor excitability of the tibialis anterior muscle [121]. Subjects who performed ten-session biofeedback balance training with inertial sensors showed a greater improvement and better compliance in balance skills than those who performed ten-session conventional balance training, indicating that the biofeedback system is probably involved in enhancing neuroplasticity to improve postural and balance in subacute stroke patients [122].

Moreover, wrist extension training that is externally paced at the preferred movement frequency promotes use-dependent plasticity [123]. Chest expansion exercise plus transcutaneous electrical nerve stimulation (TENS) may effectively improve gait ability and trunk control in chronic stroke patients [124]. Device-assisted mirror symmetrical bimanual movements for 4 weeks may accelerate upper limb function recovery at the subacute stage following first-ever ischemic stroke [125]. Participation in a comprehensive rehabilitation program for 25 days during the subacute stroke phase was shown to have an important effect on upper limb function. Compared with men, women obtained better functional rehabilitation in all of the parameters [126]. Video games can induce neuroplasticity

and provide a beneficial environment in which patients can perform repetitive, functionally meaningful movements. Video games are designed to focus on several fundamental principles, including reward, challenge, goals, and meaningful play, which are important to rehabilitation [127].

In summary, skilled reaching training might have a better effect on motor function improvement as compared with running exercise. Voluntary and forced exercise might not induce significantly different alterations in neuroplasticity. There are many other types of exercise therapies such as device-assisted mirror symmetrical bimanual movements, biofeedback balance training, and video games, which have been proven to exert beneficial effects in post-stroke patients in clinic.

High-, Moderate-, and Low-Intensity Exercise

The intensity of exercise might contribute to the recovery of neural function after stroke. Exercise is commonly divided into three intensities: high, moderate, and low intensity. The related clinical studies and animal experiments have been presented as shown below.

A meta-analysis suggested that HIT as a novel intervention might be safe for cardiopulmonary rehabilitation following stroke and is beneficial for cardiorespiratory fitness in post-stroke survivors [16]. High-intensity interval training of the neurologically less affected arm for 5 weeks contributes to improving cortical and spinal plasticity and bilateral strength in chronic stroke participants [128]. A maximal graded exercise test may trigger only slight changes in neuroplasticity in post-stroke patients. However, a single-bout high-intensity training (HIT) initiated immediately following practicing a motor skill may promote improvements in skill retention, probably accelerating motor recovery [129]. In a clinical study, patients with moderate hemiparesis after chronic stroke receiving low assistance (55% success at hitting targets) or high assistance (82% success at hitting targets) showed significant improvements in self-efficacy of hand function, depression, and impairment-based and functional motor outcomes following chronic stroke at the 1-month follow-up, but the high assistance group showed better improvements in motor outcomes, particularly for subjects with more severe finger motor dysfunction [130].

Compared with moderate- or low-intensity exercise, HIT is more effective for neurological function recovery after stroke, as discussed by a systematic review [15]. Moderate-intensity training (MIT) is a potential rehabilitative therapy for improving mobility and exercise capacity following stroke by regulating neuronal plasticity and inflammatory processes [131]. A meta-analysis showed that low-intensity CIMT might have more beneficial effects than high-intensity CIMT in the acute or subacute stage of stroke [120].

In animal experiment, low-volume HIT might be more effective than MIT in promoting brain plasticity after ischemic stroke, as it results in more effective motor function improvement [132], possibly through an increase in the ratio of mBDNF/proBDNF in the hippocampus [74]. In addition, compared with those that undergo high-intensity exercise, rats that undergo low-intensity exercise exhibit better spatial memory performance and obviously increased dendritic complexity in the bilateral hippocampus [53].

As noted above, HIT has better benefits for stroke-induced dysfunction than moderate- and low-intensity training. For individuals, neuroplasticity is likely dependent on exercise intensity. The increased number of changes in neuroplasticity caused by high-intensity exercise can lead to better neural function recovery. Moreover, low-intensity exercise might

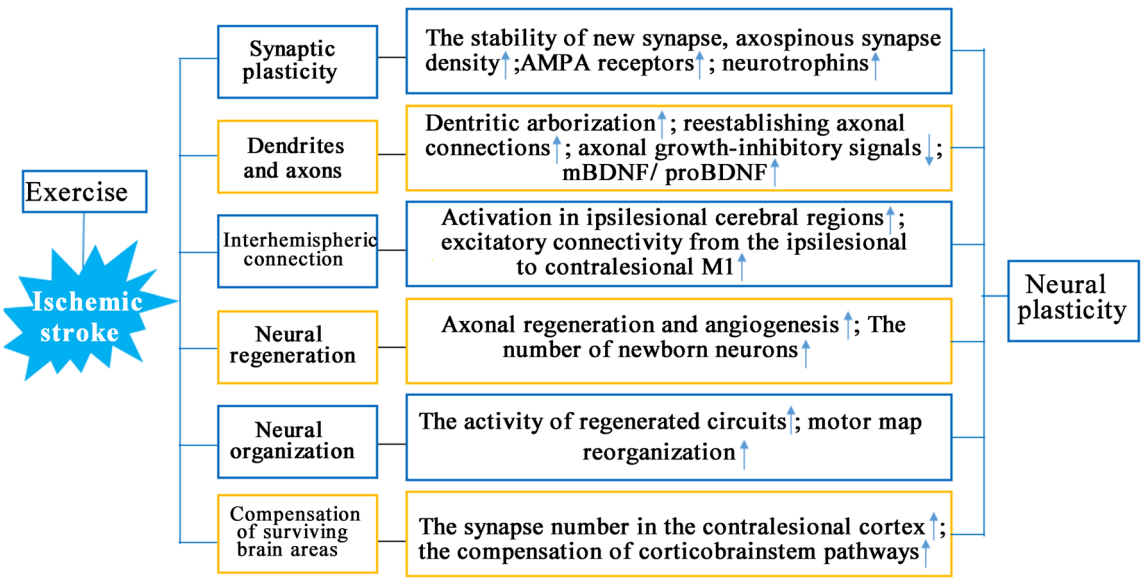

Fig. 1 The mechanisms of exercise-induced neuroplasticity after ischemic stroke

exhibit better spatial memory performance in ischemic rats and exert more beneficial effects than HIT in the patients of acute or subacute stage of stroke. Thereby, the effects of high-, moderate-, and low-intensity exercise in patients and animals remain to be explored.

Robot-Assisted Movement, a Novel Exercise Method

Robot-assisted movement is increasingly being applied for rehabilitation therapy in post-stroke patients. Clinical testing on 10 acute stroke survivors showed that a wearable robotic device promoted isometric torque generation. Early in-bed rehabilitation using a wearable robotic device combined with active and passive movement training contributed to improving motor control ability and promoting neuroplasticity [133]. Robot-assisted training for 1 month can improve crucial psychological outcomes, including motor learning and memory in patients with chronic stroke, and its effectiveness appears to result at least partially from proprioceptive stimulation [130].

Task-oriented rehabilitation robotics is the most promising approach and is based on the current concepts of practice-induced neuroplasticity and motor control/learning. Its clinical application focuses on grasping and manipulating task training using commercially available tactual robotic devices [134]. In a clinical study, patients received training at home with an MR-compatible hand-induced robotic device. Functional magnetic resonance imaging (fMRI) results revealed connectivity alterations in the premotor cortex, cerebellum, M1, and supplementary motor area (SMA), suggesting that M1 dysfunction can benefit from the enhancement of SMA activity. Therefore, connectivity alterations in motor areas might contribute to improvements in the functionally abnormal M1 in post-stroke survivors with motor dysfunction [135].

In summary, robot-assisted therapy is effective in improving upper limb motor function, learning, and memory in stroke patients, and the possible mechanism involves improving neuroplasticity.

Conclusion

Herein, we discussed recent studies on the mechanisms of exercise-induced neuroplasticity after stroke, analyzed the application of exercise rehabilitation, and discussed a novel exercise therapy for motor and cognitive recovery after ischemic stroke related to influencing neuroplasticity. As shown in Fig. 1, exercise facilitates neuroplasticity in multiple ways, including by promoting the compensation of surviving brain areas; improving interhemispheric connections; increasing synaptic plasticity through regulating neurotrophins, synaptic activity, and structure; and accelerating neuronal reorganization and regeneration. Based on research on neuroplasticity in the brain, exercise rehabilitation targeting neuroplasticity is an area that requires further research to improve neuronal function after stroke. In addition, robot-assisted therapy is effective in improving upper limb motor function, learning, and memory in stroke patients, and the possible mechanism involves facilitating neuroplasticity. This type of novel exercise therapy should be widely applied in the clinic worldwide to help stroke patients.

Author Contributions Ying Xing prepared figures and drafted the manuscript; Ying Xing and Yulong Bai edited and revised the manuscript; Yulong Bai approved the final version of the manuscript.

Funding Information This work was supported by the National Natural Science Foundation of China (No. 81871841).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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