Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_63_20

Mini Review (Part I): An Experimental Concept on Exercise and Ischemic Conditioning in Stroke Rehabilitation

Qingzhu Wang[1], Melissa Wills[2], Zhenzhen Han[1,3], Xiaokun Geng[1,2,3], Yuchuan Ding[3,4]

Abstract:

Stroke remains a leading cause of adult death and disability. Poststroke rehabilitation is vital for reducing the long-term sequelae of brain ischemia. Recently, physical exercise training has been well established as an effective rehabilitation tool, but its efficacy depends on exercise parameters and the patient's capacities, which are often altered following a major cerebrovascular event. Thus, ischemic conditioning as a rehabilitation intervention was considered an "exercise equivalent," but the investigation is still in its relative infancy. In this mini-review, we discuss the potential for physical exercise or ischemic conditioning and its relation to angiogenesis, neurogenesis, and plasticity in stroke rehabilitation. This allows the readers to understand the context of the research and the application of ischemic conditioning in poststroke rehabilitation.

Keywords:

Ischemic conditioning, physical exercise, stroke rehabilitation

[1]China-America Institute of Neuroscience, Beijing Luhe Hospital, Capital Medical University, [3]Department of Neurology, Beijing Luhe Hospital, Capital Medical University, Beijing, China, [2]Department of Neurosurgery, Wayne State University School of Medicine, [4]Department of Research and Development Center, John D. Dingell VA Medical Center, Detroit, Michigan, USA

Address for correspondence:
Dr. Xiaokun Geng, Department of Neurology, Beijing Luhe Hospital, Capital Medical University, No. 82 Xinhua South Road, Tongzhou District, Beijing 101149, China.
E-mail: xgeng@ccmu.edu.cn

Submission: 10-11-2020
Revised: 10-12-2020
Accepted: 11-12-2020
Published: 29-12-2020

Introduction

Stroke is a leading cause of adult death and disability worldwide.[1,2] Consequently, it is vital to improve the quality of life and functional prognosis of stroke victims. Stroke rehabilitation is the medical specialty that integrates a variety of techniques to maximize patient recovery following a stroke.[3,4] Recent research indicates that increases in angiogenesis, neurogenesis, and plasticity such as synaptogenesis, dendrite remodeling, and axonal reorganization occur during the recovery phase after a stroke.[5-7] Modulating and optimizing these processes of the recovery phase can minimize functional loss and enhance rehabilitation in patients who have experienced stroke. Physical exercise is a behavioral intervention that is known to enhance stroke rehabilitation through biochemical mechanisms.[8,9] However, the benefits of physical exercise are variable and are highly dependent on the patient's abilities, which can be limited by the early complications of a stroke. Moreover, ischemic conditioning has been proposed as an accessible therapy that could confer the benefits of exercise with minimal dependence on these limitations.[6] Both of these nonpharmacological techniques for rehabilitation are low cost and noninvasive, and therefore merit to have their benefits explored in great depth. This mini-review intends to discuss the potential for physical exercise or ischemic conditioning and its relation to angiogenesis, neurogenesis, and plasticity in stroke rehabilitation, as well as elucidate the potential for clinical application.

Effect of Physical Exercise on Neurorehabilitation

Neurorehabilitation

Physical exercise can play a major nonpharmacological role in the rehabilitation

How to cite this article: Wang Q, Wills M, Han Z, Geng X, Ding Y. Mini review (Part I): An experimental concept on exercise and ischemic conditioning in stroke rehabilitation. Brain Circ 2020;6:242-7.

of the poststroke patient, as it can protect against plasticity impairments caused by the stroke as well as stimulate angiogenesis and neurogenesis.[10-12] Ding lab reported that motor training, particularly motor skill training involving balance and coordination, facilitates a uniquely lateralized synaptogenesis in the thalamus. Analogously, involuntary, voluntary, and forced exercises induced high expressions of postsynaptic density 95 (PSD-95), synapsin I (SYN), microtubule-associated protein 2 (MAP-2), and Tau, thereby reducing the loss of dendrons and neurons in the hippocampus after stroke and improving cognition.[13] PSD-95, SYN, MAP-2, and Tau were identified as the markers of synaptogenesis.[14-16] In addition, Song-Hee Cheon and Mizutani proposed that physical exercise increased the expression of growth-associated protein 43 (GAP-43), a known plasticity protein,[17] in the hippocampus or cortex surrounding the ischemia and resulted in enhanced cognition and better functional rehabilitation.[18,19] Likewise, treadmill exercise promoted both synaptogenesis and axonal growth through synaptosomal-associated protein-25 and glial fibrillary acidic protein expression in the cerebellum and thereby improved motor coordination.[20] Previous studies have found that forced exercise at moderate to high intensity increases brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), nerve growth factor (NGF), and vascular endothelial cell growth factor (VEGF) in multiple brain regions at least in animal models of stroke.[21-23] BDNF, IGF-I, NGF, and VEGF confer neuroplasticity and promote neurogenesis and cerebral angiogenesis.[21,24] In addition, treadmill exercise was found to significantly the expression of CD200 and CD200R, which are known to inhibit microglial activation and inflammation and promote neurogenesis, within the hippocampus and cortex.[25] These findings highlight the benefit of physical exercise in poststroke rehabilitation and the nuances suggest that various forms of exercise may be beneficial for the rehabilitation of specific cerebral structures and may therefore be preferentially applied to patients depending on the nature of their cerebrovascular accident.

Double-edge sword of exercise in rehabilitation

When the *in vitro* results are applied in the clinical setting, the efficacy of physical exercise rehabilitation is dependent on other variables, such as temporal measures and the types of training strategies employed.[26] For example, global indices of disability have shown a tendency to improve after cardiorespiratory training, which may be mediated by improved mobility and balance, whereas interventions that employ resistance training have less reliably shown benefits.[27]

Consequently, the volume, intensity, and exercise session frequency as well as initiation time must be optimized.[10] Our study recently suggested that the beneficial effect of intense exercise was not superior than its milder counterpart, thus mild exercise may be adequate and sufficient to elicit neurorehabilitation poststroke.[28] Our previous study underlined that too early poststroke exercise increased cell stress and expression of pro-inflammatory cytokines, which amplified tissue damage, and suggests that exercise interventions between 24 h and 3 days may optimize rehabilitation benefit.[29] In addition, Yagita *et al*. suggested that running as a form of exercise may be too intense and cause spikes in endogenous corticosteroid levels that limit poststroke neurogenesis.[30] Moreover, complex and variable poststroke disability could limit patients' participation.[31] The amenability of patients to poststroke physical activity may vary in relation to age, motivation, and other factors, and may be significantly affected by the level of disability conferred from the cerebrovascular accident. These differences within the patient population could limit efforts to standardize and optimize care for these patients. For example, patients with anterior cerebral artery infarcts may lose the ability to ambulate, whereas those with middle cerebral artery infarcts may be unable to move the upper limbs. As such, different exercise protocols must be explored to accommodate patients based on the type and extent of injury. Moreover, recent clinical trials do not show consistent rehabilitative benefits in stroke patients undergoing early physical exercise.[32-34] Therefore, an alternative intervention known as ischemic conditioning, which confers similar neuroplastic benefits with fewer interuser particularities, is of interest to our group.

Ischemic Conditioning and Neurorehabilitation

Neuroprotection

Recently, ischemic conditioning has emerged as a noninvasive and low-cost therapy for victims of cerebrovascular accidents. By way of controlled and transient periods of subcritical ischemia to nonvital arteries,[35,36] it works to activate endogenous tissue repair mechanisms to exert neuroprotective effects, cardiovascular protection, and promote neurological recovery.[37,38] Ji lab reported that repetitive bilateral arm ischemic preconditioning (BAIPC) safely inhibited stroke recurrence and enhanced tolerance of cerebral ischemia, by improving cerebral perfusion and attenuating inflammation and coagulation in patients with symptomatic intracranial arterial stenosis for all ages.[39,40] In the molecular events, ischemic postconditioning was found to restore voltage-dependent anion channel proteins (VDACs) to protect against mitochondrial damage.[41,42] Brain ischemic preconditioning was demonstrated to protect blood–brain barrier against ischemic injury by activation of the nuclear

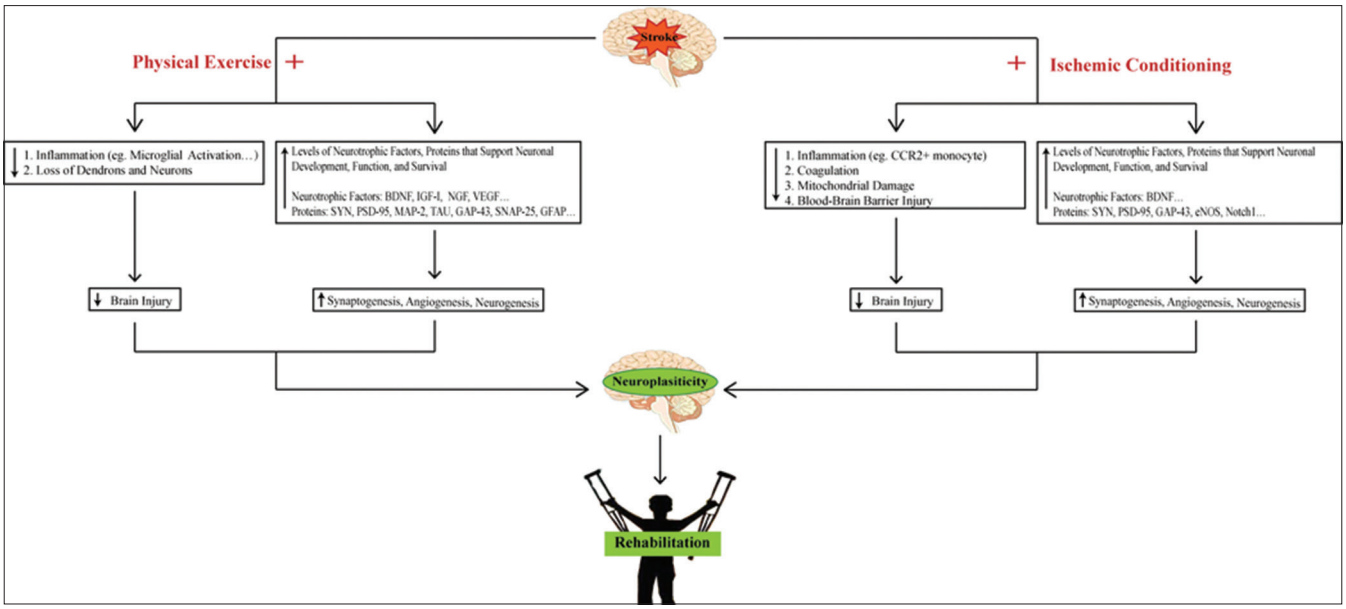

Figure 1: Physical exercise and ischemic conditioning favorably decrease brain damage and stimulate synaptogenesis, angiogenesis, and neurogenesis to enhance neuroplasticity, which promotes poststroke rehabilitation. Some underlying mechanisms of exercise and ischemic conditioning have been evidenced to overlap – both therapies demonstrate regulation of the immune and inflammatory system and upregulated the expression of SYN1, PSD95, growth-associated protein 43, and brain-derived neurotrophic factor

factor (erythroid-derived 2)-like 2 (Nrf2) pathway.[43] Esposito *et al.* have found that ischemic conditioning significantly reduced infarction, improved neurological outcomes, and involved the promotion of neurogenesis and angiogenic remodeling during the recovery phase after focal cerebral ischemia.[6] The combination of early and delayed ischemic postconditioning may activate ERK1/2 and CREB and induce the production of BDNF in neurons and astrocytes lead to long-term potentiation and neurogenesis, which highlights the neuroprotective potential of these therapies.[6,44] Likewise, Ramagiri indicated that remote ischemic postconditioning (RIPostC) alleviated cerebral ischemic-reperfusion injury and exerted neuroprotective effects through the GSK-3 β/CREB/BDNF pathway, which is known to be involved in cell survival and metabolism during stress.[45-47] RIPostC promoted cognition mediated by endothelial nitric oxide synthase (eNOS)-dependent augmentation of angiogenesis.[48,49] Furthermore, ischemic conditioning after stroke upregulated the expression of SYN1, PSD95, and GAP43, which are also key players in the context of exercise therapy, and promoted neuroprotection and plasticity.[17,50,51] Doeppner *et al.* found that ischemic conditioning enhanced neurological recovery and neuronal survival in response to neural precursor cell transplantation, which could stimulate brain plasticity.[52,53] Similarly, astrocytes play an important role in developmental synaptogenesis and blood–brain barrier modulation and RIPostC could regulate its activity and inhibit STAT3 phosphorylation to promote neurological function recovery.[54] Moreover, it was proposed that ischemic conditioning could stimulate arteriogenesis and enhance cerebral blood flow by increasing expressions of Notch1 and Notch intracellular domain (NICD) in the ischemic brain.[55] Arteriogenesis plays a vital role in regulating vascular recovery of neurological function.[56]

Neurorehabilitation and plasticity

Recent studies demonstrate that ischemic conditioning may induce neurorehabilitation through similar mechanisms as physical exercise. In contrast to physical therapy, the passive nature of ischemic conditioning allows less dependence on the patient's motivation and level of physical activity and is not limited by poststroke disability. In addition, it is less likely to be harmful or present risk to the patient.[57] The investigation of ischemic conditioning as a therapy for stroke recovery is still in its relative infancy, especially when compared to that of its cardioprotective effects.[58,59] The patients of noncardiac ischemic stroke received RIPostC were demonstrated to improve significantly in cognitive domains, such as visuospatial and executive functioning and attention 6 months poststroke.[60] Pilot studies showed that ischemic conditioning increased the paretic leg strength and muscle activation and improved self-selected walking speed of chronic stroke survivors.[61,62] Doeppner *et al*. showed that very delayed RIPostC started on day 5 after stroke induction stimulated angioneurogenesis and reversed immunosuppression occur to induce sustained neurological recovery.[37] Vaibhav *et al*. found that RIPostC mediated neurological recovery after ICH through AMPK-dependent immune

regulation.[63] During the recovery phase, RIPostC increased a pro-inflammatory CCR2 + monocyte subset to improve outcomes.[64] Taken together, ischemic conditioning was considered an "exercise equivalent" as a rehabilitation intervention. However, a plethora of questions remains regarding ischemic conditioning in the setting of stroke rehabilitation. Since the clinical research of ischemic therapy is still in its infancy, investigation efforts are not standardized in the precise methods in which they deliver the therapy or monitor results. They vary by the type of vessel occluded and the duration and frequency of therapy. Future directions are essential to optimize these parameters to maximize poststroke cerebral angiogenesis and neurogenesis and should also consider how treatment will vary with the individuality of the patient.

Conclusion and Prospective

Based on current research, physical exercise and ischemic conditioning favorably induce neuroprotection to decrease brain damage after stroke, as well as stimulate neuroplasticity, angiogenesis, and neurogenesis, which is conducive to poststroke rehabilitation [Figure 1]. More research is required to investigate the precise benefits and application of poststroke exercise therapy, especially in the context of patient individualities. However, compared to physical exercise, a paucity of data exists regarding the efficacy and underlying cellular mechanism of ischemic conditioning in poststroke rehabilitation. A larger number of well-organized animal and *in vitro* experiments are needed to further compare the efficacy of physical exercise and ischemic conditioning to discuss if ischemic conditioning could be an adequate substitute for physical exercise in stroke patients. Moreover, it is necessary to establish long-term and large preclinical and clinical trials with sufficient sample sizes and multidisciplinary research to further explore the optimal parameters of physical exercise and ischemic conditioning and to avoid undesirable effects.

Financial support and sponsorship

This work was partially supported by the National Natural Science Foundation of China (8207091513, 8187090351, 8200090876, 8180090323), the Beijing Tongzhou District Financial Fund, the Science and Technology Plan of Beijing Tongzhou District (KJ2020CX002).

Conflicts of interest

There are no conflicts of interest.

References

1. Veldema J, Jansen P. Ergometer training in stroke rehabilitation: Systematic review and meta-analysis. Arch Phys Med Rehabil 2020;101:674-89.
2. Stone CR, Geng X, Ding Y. From big data to battling disease: Notes from the frontiers of cerebrovascular science. Neurol Res 2019;41:679-80.
3. O'Dell MW, Lin CC, Harrison V. Stroke rehabilitation: Strategies to enhance motor recovery. Annu Rev Med 2009;60:55-68.
4. Jindal S. Remodeling in asthma and COPD-recent concepts. Lung India 2015;1:1-2.
5. Sampaio-Baptista C, Sanders ZB, Johansen-Berg H. Structural plasticity in adulthood with motor learning and stroke rehabilitation. Annu Rev Neurosci 2018;41:25-40.
6. Esposito E, Hayakawa K, Maki T, Arai K, Lo EH. Effects of postconditioning on neurogenesis and angiogenesis during the recovery phase after focal cerebral ischemia. Stroke 2015;46:2691-4.
7. Ren C, Li N, Gao C, Zhang W, Yang Y, Li S, *et al.* Ligustilide provides neuroprotection by promoting angiogenesis after cerebral ischemia. Neurol Res 2020;42:683-92.
8. Gallanagh S, Quinn TJ, Alexander J, Walters MR. Physical activity in the prevention and treatment of stroke. ISRN Neurol 2011;2011:953818.
9. Zhang H, Lee JY, Borlongan CV, Tajiri N. A brief physical activity protects against ischemic stroke. Brain Circ 2019;5:112-8.
10. Pin-Barre C, Laurin J. Physical exercise as a diagnostic, rehabilitation, and preventive tool: Influence on neuroplasticity and motor recovery after stroke. Neural Plast 2015;2015:608581.
11. Kalogeraki E, Pielecka-Fortuna J, Hüppe JM, Löwel S. Physical exercise preserves adult visual plasticity in mice and restores it after a stroke in the somatosensory cortex. Front Aging Neurosci 2016;8:212.
12. Elzib H, Pawloski J, Ding Y, Asmaro K. Antidepressant pharmacotherapy and poststroke motor rehabilitation: A review of neurophysiologic mechanisms and clinical relevance. Brain Circ 2019;5:62-7.
13. Ding Y, Li J, Clark J, Diaz FG, Rafols JA. Synaptic plasticity in thalamic nuclei enhanced by motor skill training in rat with transient middle cerebral artery occlusion. Neurol Res 2003;25:189-94.
14. Won S, Incontro S, Nicoll RA, Roche KW. PSD-95 stabilizes NMDA receptors by inducing the degradation of STEP61. Proc Natl Acad Sci U S A 2016;113:E4736-44.
15. Gudi V, Gai L, Herder V, Tejedor LS, Kipp M, Amor S, *et al.* Synaptophysin is a reliable marker for axonal damage. J Neuropathol Exp Neurol 2017;76:109-25.
16. Hulsebosch CE, DeWitt DS, Jenkins LW, Prough DS. Traumatic brain injury in rats results in increased expression of gap-43 that correlates with behavioral recovery. Neurosci Lett 1998;255:83-6.
17. Carmichael ST. Plasticity of cortical projections after stroke. Neuroscientist 2003;9:64-75.
18. Cheon SH. The effect of a skilled reaching task on hippocampal plasticity after intracerebral hemorrhage in adult rats. J Phys Ther Sci 2015;27:131-3.
19. Mizutani K, Sonoda S, Wakita H. Ritanserin, a serotonin-2 receptor antagonist, inhibits functional recovery after cerebral infarction. Neuroreport 2018;29:54-8.
20. Mizutani K, Sonoda S, Hayashi N, Takasaki A, Beppu H, Saitoh E, *et al.* Analysis of protein expression profile in the cerebellum of cerebral infarction rats after treadmill training. Am J Phys Med Rehabil 2010;89:107-14.
21. Ploughman M, Austin MW, Glynn L, Corbett D. The effects of poststroke aerobic exercise on neuroplasticity: A systematic review of animal and clinical studies. Transl Stroke Res 2015;6:13-28.
22. Pang Q, Zhang H, Chen Z, Wu Y, Bai M, Liu Y, *et al.* Role of caveolin-1/vascular endothelial growth factor pathway in basic fibroblast growth factor-induced angiogenesis and neurogenesis after treadmill training following focal cerebral ischemia in rats. Brain Res 2017;1663:9-19.
23. Ke Z, Yip SP, Li L, Zheng XX, Tong KY. The effects of voluntary, involuntary, and forced exercises on brain-derived neurotrophic

factor and motor function recovery: A rat brain ischemia model. PLoS One 2011;6:e16643.
24. Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, *et al.* VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. J Clin Invest 2003;111:1843-51.
25. Sun H, Li A, Hou T, Tao X, Chen M, Wu C, *et al.* Neurogenesis promoted by the CD200/CD200R signaling pathway following treadmill exercise enhances post-stroke functional recovery in rats. Brain Behav Immun 2019;82:354-71.
26. Schmidt A, Wellmann J, Schilling M, Strecker JK, Sommer C, Schäbitz WR, *et al.* Meta-analysis of the efficacy of different training strategies in animal models of ischemic stroke. Stroke 2014;45:239-47.
27. Saunders DH, Sanderson M, Hayes S, Kilrane M, Greig CA, Brazzelli M, *et al.* Physical fitness training for stroke patients. Cochrane Database Syst Rev 2016;3:CD003316.
28. Li F, Geng X, Huber C, Stone C, Ding Y. In search of a dose: The functional and molecular effects of exercise on post-stroke rehabilitation in rats. Front Cell Neurosci 2020;14:186.
29. Li F, Pendy JT, Jr., Ding JN, Peng C, Li X, Shen J, *et al*. Exercise rehabilitation immediately following ischemic stroke exacerbates inflammatory injury. Neurol Res 2017;39:530-7.
30. Yagita Y, Kitagawa K, Sasaki T, Terasaki Y, Todo K, Omura-Matsuoka E, *et al.* Postischemic exercise decreases neurogenesis in the adult rat dentate gyrus. Neurosci Lett 2006;409:24-9.
31. Saunders DH, Greig CA, Mead GE. Physical activity and exercise after stroke: Review of multiple meaningful benefits. Stroke 2014;45:3742-7.
32. Cumming TB, Tyedin K, Churilov L, Morris ME, Bernhardt J. The effect of physical activity on cognitive function after stroke: A systematic review. Int Psychogeriatr 2012;24:557-67.
33. Yelnik AP, Quintaine V, Andriantsifanetra C, Wannepain M, Reiner P, Marnef H, *et al.* AMOBES (Active mobility very early after stroke): A randomized controlled trial. Stroke 2017;48:400-5.
34. Cumming TB, Bernhardt J, Lowe D, Collier J, Dewey H, Langhorne P, *et al*. Early mobilization after stroke is not associated with cognitive outcome. Stroke 2018;49:2147-54.
35. Ramagiri S, Taliyan R. Remote limb ischemic post conditioning during early reperfusion alleviates cerebral ischemic reperfusion injury via gsk-3beta/creb/bdnf pathway. Eur J Pharmacol 2017;803:84-93.
36. Sangeetha RP, Ramesh VJ, Kamath S, Christopher R, Bhat DI, Arvinda HR, *et al.* Effect of remote ischemic preconditioning on cerebral vasospasm and biomarkers of cerebral ischemia in aneurysmal subarachnoid hemorrhage (ERVAS): A protocol for a randomized, controlled pilot trial. Brain Circ 2019;5:12-8.
37. Doeppner TR, Zechmeister B, Kaltwasser B, Jin F, Zheng X, Majid A, *et al.* Very delayed remote ischemic post-conditioning induces sustained neurological recovery by mechanisms involving enhanced angioneurogenesis and peripheral immunosuppression reversal. Front Cell Neurosci 2018;12:383.
38. Gidday Jm. Cerebrovascular ischemic protection by pre- and post-conditioning. Brain Circ 2015;1:97-103.
39. Meng R, Ding Y, Asmaro K, Brogan D, Meng L, Sui M, *et al.* Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. Neurotherapeutics 2015;12:667-77.
40. Schimmel Sj, Acosta S, Lozano D. Neuroinflammation in traumatic brain injury: A chronic response to an acute injury. Brain Circ 2017;3:135-42.
41. Yao GY, Zhu Q, Xia J, Chen FJ, Huang M, Liu J, *et al.* Ischemic postconditioning confers cerebroprotection by stabilizing VDACs after brain ischemia. Cell Death Dis 2018;9:1033.
42. Russo E, Nguyen H, Lippert T, Tuazon J, Borlongan CV, Napoli E, *et al.* Mitochondrial targeting as a novel therapy for stroke. Brain Circ 2018;4:84-94.
43. Yang T, Sun Y, Mao L, Zhang M, Li Q, Zhang L, *et al*. Brain ischemic preconditioning protects against ischemic injury and preserves the blood-brain barrier via oxidative signaling and nrf2 activation. Redox BioL 2018;17:323-37.
44. Wu H, Yang SF, Dai J, Qiu YM, Miao YF, Zhang XH, *et al.* Combination of early and delayed ischemic postconditioning enhances brain-derived neurotrophic factor production by upregulating the ERK-CREB pathway in rats with focal ischemia. Mol Med Rep 2015;12:6427-34.
45. Zhao H, Sapolsky RM, Steinberg GK. Phosphoinositide-3-kinase/akt survival signal pathways are implicated in neuronal survival after stroke. Mol Neurobiol 2006;34:249-70.
46. Ramagiri S, Taliyan R. Remote limb ischemic post conditioning during early reperfusion alleviates cerebral ischemic reperfusion injury via GSK-3B/CREB/BDNF pathway. Eur J Pharmacol 2017;803:84-93.
47. Han R, Liu Z, Sun N, Liu S, Li L, Shen Y, I. BDNF alleviates neuroinflammation in the hippocampus of type 1 diabetic mice via blocking the aberrant HMGB1/RAGE/NF-κb pathway. Aging Dis 2019;10:611-625.
48. Ren C, Li N, Li S, Han R, Huang Q, Hu J, *et al.* Limb ischemic conditioning improved cognitive deficits via eNOS-dependent augmentation of angiogenesis after chronic cerebral hypoperfusion in rats. Aging Dis 2018;9:869-79.
49. Iqbal S, Hayman EG, Hong C, Stokum JA, Kurland DB, Gerzanich V, *et al.* Inducible nitric oxide synthase (NOS-2) in subarachnoid hemorrhage: Regulatory mechanisms and therapeutic implications. Brain Circ 2016;2:8-19.
50. Xie R, Wang P, Ji X, Zhao H. Ischemic post-conditioning facilitates brain recovery after stroke by promoting akt/mTOR activity in nude rats. J Neurochem 2013;127:723-32.
51. Wang Y, Zhang Z, Zhang L, Yang H, Shen Z. RLIPostC protects against cerebral ischemia through improved synaptogenesis in rats. Brain Inj 2018;32:1429-36.
52. Hermann DM, Chopp M. Promoting brain remodelling and plasticity for stroke recovery: Therapeutic promise and potential pitfalls of clinical translation. Lancet Neurol 2012;11:369-80.
53. Doeppner TR, Doehring M, Kaltwasser B, Majid A, Lin F, Bähr M, *et al.* Ischemic post-conditioning induces post-stroke neuroprotection via hsp70-mediated proteasome inhibition and facilitates neural progenitor cell transplantation. Mol Neurobiol 2017;54:6061-73.
54. Cheng X, Zhao H, Yan F, Tao Z, Wang R, Han Z, *et al.* Limb remote ischemic post-conditioning mitigates brain recovery in a mouse model of ischemic stroke by regulating reactive astrocytic plasticity. Brain Res 2018;1686:94-100.
55. Ren C, Li S, Wang B, Han R, Li N, Gao J, *et al.* Limb remote ischemic conditioning increases notch signaling activity and promotes arteriogenesis in the ischemic rat brain. Behav Brain Res 2018;340:87-93.
56. Thored P, Wood J, Arvidsson A, Cammenga J, Kokaia Z, Lindvall O, *et al.* Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. Stroke 2007;38:3032-9.
57. Zhao W, Li S, Ren C, Meng R, Jin K, Ji X, *et al.* Remote ischemic conditioning for stroke: Clinical data, challenges, and future directions. Ann Clin Transl Neurol 2019;6:186-96.
58. Heusch G. Molecular basis of cardioprotection: Signal transduction in ischemic pre-, post-, and remote conditioning. Circ Res 2015;116:674-99.
59. Aimo A, Borrelli C, Giannoni A, Pastormerlo LE, Barison A, Mirizzi G, *et al*. Cardioprotection by remote ischemic conditioning: Mechanisms and clinical evidences. World J Cardiol 2015;7:621-32.
60. Feng X, Huang L, Wang Z, Wang L, Du X, Wang Q, *et al.* Efficacy of remote limb ischemic conditioning on poststroke cognitive impairment. J Integr Neurosci 2019;18:377-85.

61. Hyngstrom AS, Murphy SA, Nguyen J, Schmit BD, Negro F, Gutterman DD, *et al.* Ischemic conditioning increases strength and volitional activation of paretic muscle in chronic stroke: A pilot study. J Appl Physiol (1985) 2018;124:1140-7.
62. Durand MJ, Boerger TF, Nguyen JN, Alqahtani SZ, Wright MT, Schmit BD, *et al.* Two weeks of ischemic conditioning improves walking speed and reduces neuromuscular fatigability in chronic stroke survivors. J Appl Physiol (1985) 2019;126:755-63.
63. Vaibhav K, Braun M, Khan MB, Fatima S, Saad N, Shankar A, *et al.* Remote ischemic post-conditioning promotes hematoma resolution via AMPK-dependent immune regulation. J Exp Med 2018;215:2636-54.
64. Yang J, Balkaya M, Beltran C, Heo JH, Cho S. Remote postischemic conditioning promotes stroke recovery by shifting circulating monocytes to ccr2(+) proinflammatory subset. J Neurosci: The Official Journal of the Society for Neuroscience 2019;39:7778-89.