PHYSICAL
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REVIEW

Endogenous neuroprotective potential due to preconditioning exercise in stroke

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ABSTRACT. Stroke is a leading cause of serious long-term physical disability due to insufficient neurorepair mechanisms. In general, physical activity is an important modifiable risk factor, particularly for stroke and cardiovascular diseases. Physical exercise has shown to be neuroprotective in both animal experiments and clinical settings. Exercise can be considered a mild stressor and follows the prototypical preconditioning stimulus. It has beneficial effects on brain health and cognitive function. Preconditioning exercise, which is prophylactic exercise prior to ischemia, can protect the brain from subsequent serious injury through promotion of angiogenesis, mediation of inflammatory responses, inhibition of glutamate over-activation, protection of the blood-brain barrier, and inhibition of apoptosis. Preconditioning exercise appears to induce brain ischemic tolerance and it has been shown to exert beneficial effects. It is clinically safe and feasible and represents an exciting new paradigm in endogenous neuroprotection for patients with acute stroke. In this review, we describe the neuroprotective potential of preconditioning exercise and clinical applications in patients with acute ischemic stroke.

Key words: preconditioning exercise, rehabilitation, stroke, neuroprotection

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Stroke is a leading cause of serious long-term physical disability. Stroke survivors worldwide experience disability and severe morbidity due to motor and cognitive deficits. Since 1995, intravenous thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA) has been a recommended medical therapy for acute ischemic stroke[1]. Unfortunately, due to difficulties in differentiating etiology and a limited therapeutic time window, rt-PA is available to only 3%-5% of the patients with stroke[2,3]. Although rehabilitation interventions improve the outcome, full recovery is often not achieved[4].

Exercise is one of the several behavioral interventions that influence neurotrophins, neuroplasticity, and cognition[5]. In addition, regular exercise promotes general health and reduces the risk of hypokinetic disease-associated sedentary lifestyle[6]. Furthermore, regular exercise ameliorates abnormal arterial blood pressure, improves glucose and lipid metabolic disorders, reduces obesity and improves endothelial function[7]. Exercise enhances neurobiological processes that promote brain health in aging and disease, thus resulting in systemic beneficial effects, including the promotion of brain function[6,8]. It has strong effects on the immune system and alters the production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)[8]. Moreover, exercise may protect the brain against degenerative events by increasing the expression of brain-derived neurotrophic factor (BDNF) in the brain and insulin-like growth factor-1 (IGF-1) in the blood[9,10]. A recent study has demonstrated that exercise-induced hormone irisin contributes to the neuroprotective effect of physical exercise against cerebral ischemia[11]. Exercise, even of moderate intensity, has systemic effects on the body, including the central nervous system[8].

Animal studies have demonstrated the beneficial effects of exercise on cerebral ischemia, including amelioration of blood-brain barrier (BBB) dysfunction, maintenance of neurovascular integrity, promotion of enhanced cell survival, and fewer neurological deficits[5,7,12]. There is growing literature substantiating the benefits of exercise intervention on induced brain injury in animal stroke models[13-16]. It is

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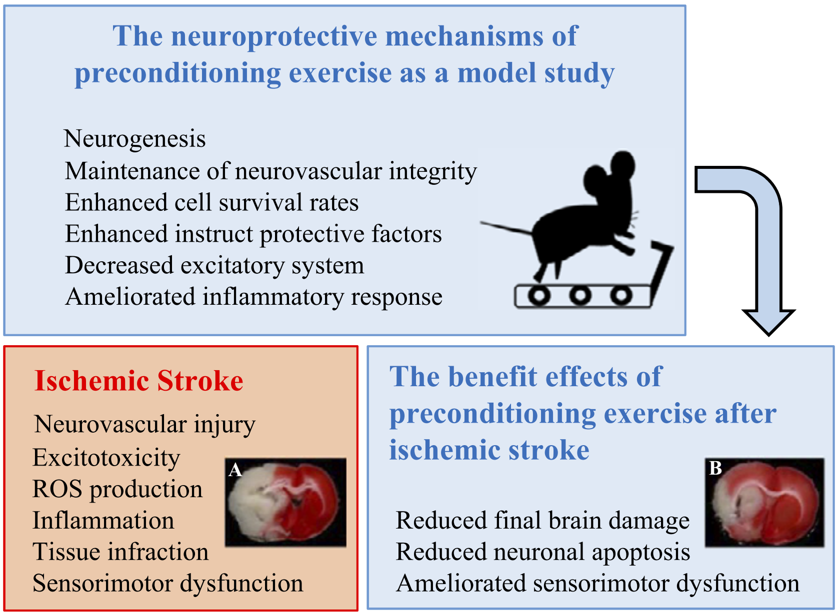

Figure 1. The neuroprotective mechanisms of preconditioning exercise in the brain. Ischemic stroke induces neurovascular injury through mechanisms such as excitotoxicity, reactive oxygen species (ROS) production, and inflammation. Preconditioning exercise, which is prophylactic exercise prior to stroke, has been shown to exert beneficial effects after stroke. In the 2,3,5-triphenyltetrazorlium chloride (TTC) study, the tissue infarction in rats with preconditioning exercise (right, white area) was decreased compared with the brain of rats without preconditioning (left).

now well-established that physical exercise can exert neuroprotection and neuroplasticity both in animal experiments and clinical settings[7]. This neuroprotective potential of prophylactic exercise as preconditioning has garnered great interest in stroke rehabilitation medicine. In this review, we consider the endogenous neuroprotective potential of preconditioning exercise, its role prior to ischemia, molecular mechanisms, and clinical application.

Exercise Prior to Ischemic Stroke (Preconditioning Exercise)

Preconditioning is defined as the exposure of a system or an organ to a conditioning stimulus to induce tolerance or resistance to a subsequent injury[17]. Moreover, preconditioning is an endogenous strategy that triggers cells and organisms to initiate the expression of intrinsic protective factors, thus helping them acquire tolerance and self-defense against subsequent damage[1]. Multiple preconditioning stimuli, such as hypoxia, ischemia, oxidative stress, anoxia, and oxidative phosphorylation inhibitors, have been studied[18]. However, such prophylactic treatments may be harmful to patients; therefore, more safer and feasible treatments have been sought recently[7]. Exercise, which can be considered a mild stressor, is a prototypical preconditioning stimulus and has beneficial effects on brain health and cognitive function[5,19].

Previous animal experiments have demonstrated the beneficial effect of preconditioning exercise on stroke-induced brain injury[7,19]. Preconditioning exercise induces a stimuli similar to ischemia in the brain before injury, which induces tolerance or resistance to the subsequent injury such as brain ischemic tolerance. Several studies have demonstrated that preconditioning exercise provides significant neuroprotection against acute stroke through the promotion of angiogenesis, mediation of inflammatory responses, and inhibition of neuronal apoptosis[20-23]. Therefore, various aspects are possibly involved in the neuroprotective mechanisms of preconditioning exercise in the central nervous system (Figure 1).

Preconditioning Exercise in Animal Models

Most animal studies have used a model of middle cerebral artery occlusion[16,24] and traumatic brain injury[25]. Methods of exercise preconditioning prior to ischemia have included forced treadmill running[16,26] and voluntary wheel running[27], both of which have shown a neuroprotective effect. Although preconditioning exercise by forced treadmill running can have beneficial effects, the stress induced by the enforcement to run is disadvantageous, thus outweighing the beneficial effects[28]. Previous studies have demonstrated that at least 2 or 3 weeks of exercise prior to ischemia is necessary to obtain a neuroprotective effect[29,30]. Forced treadmill running demands that the subjects exercise at a frequency of 30 min to 1 hour for 5-7 days per week[26]. Several studies have shown that moderate- or high-intensity running is effective in generating a neuroprotective effect compared with that generated with low-intensity exercise. Recently, our laboratory investigated the neuroprotective effects of different frequencies of preconditioning exercise on neuronal apoptosis using the expression of B-cell lymphoma 2 (Bcl-2) family members, such as anti-apoptotic protein Bcl-2, pro-apoptotic Bcl-2-associated X protein (Bax), and caspase-3, which is activated in the apoptotic cell. Our study demonstrated that high-intensity preconditioning exercise for three times or more per week can exert neuroprotective effects through the downregulation of the Bax/Bcl-2 ratio and caspase-3 activation after stroke[31]. This suggests that a frequency of at least three times per week of preconditioning exercise is necessary to obtain neuroprotective effects. Therefore, exercise as a neuroprotective preconditioning paradigm may depend on the frequency at a given exercise intensity. Therefore, exercise intensity and frequency prior to ischemia may be important contributing factors for stroke outcomes.

Potential Mechanisms of Preconditioning Exercise on Neuroprotection

Animal studies have indicated beneficial effects of preconditioning exercise on cerebral ischemia, including neurogenesis, maintenance of BBB and neurovascular integrity, enhanced cell survival rates and instruct protective factors, decreased excitatory system activation, and ameliorated inflammatory response[16,26,32-35] (Figure 1).

Preconditioning Exercise and Neurogenesis

Neurogenesis affords tolerance to brain ischemia, which potentially explains the connection between exercise and neurogenesis[36,37]. Previous studies have indicated that exercise promotes hippocampal neurogenesis and improves short-term memory and spatial and temporal function through neurogenesis and newly formed neuronal circuitry[38-40]. Exercise also increases the proliferation of neuronal stem cells around the damaged area following traumatic brain injury[41]. Taken together, these studies suggest that exercise-induced neurogenesis is a possible mechanism explaining the reduced brain damage and improved functional recovery after stroke in preconditioned patients.

Preconditioning Exercise and BBB Integrity

The hallmark of stroke injury is endothelial dysfunction leading to BBB leakage and edema. Exercise preconditioning improves different structural and functional components of the BBB. For example, pre-ischemic exercise improves BBB function and reduces cerebral edema[42,43]. Additionally, pre-ischemic exercise enhances the integrity of the basal lamina after ischemic stroke by inhibiting the overexpression of matrix metalloproteinase-9 (MMP-9)[42]. Treadmill pre-training also ameliorates brain edema by down-regulating aquaporin-4 in a rat ischemic stroke model[44]. Finally, pre-ischemic exercise alleviates BBB dysfunction through the extracellular signal regulated kinases (ERK1/2) pathway[20]. In summary, preconditioning exercise may help maintain the integrity of the BBB after stroke through several mechanisms.

Preconditioning Exercise and Neurovascular Integrity

Vascular remodeling is important in improving the outcome of stroke. Preconditioning exercise activates astrocytes and improves angiogenesis in the penumbra areas following brain ischemia[16]. This association of astroglial proliferation and angiogenesis with preconditioning exercise suggests that both astrocytes and endothelial cells participate in the formation of new blood vessels in the brain. Preconditioning exercise protects the brain from ischemia through improved cerebral blood flow and regulation of endothelin 1 (ET-1) in a rat model of ischemia[34]. Also, physical exercise increases levels of insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) in the serum or brain[9,25,45]. IGF-1 and VEGF both play a vital role in cerebral vasculature angiogenesis. Additionlly, preconditioning exercise elevates midkine (MK) levels after ischemic stroke[16], which is a heparin-binding growth factor which is neurotropic and promotes angiogenesis[46]. Taken together, these studies show that preconditioning exercise may improve cerebral blood flow and regulate angiogenesis of cerebral vasculature following experimentally induced ischemic stroke.

Preconditioning Exercise and Cell Survival Activity

Preconditioning exercise enhances cell survival rates in the penumbral region surrounding ischemia in a model of rat stroke[16]. The ischemic core consists of tissue necrosis, while the penumbra region surrounding the core shows signs of apoptosis. Thus, the penumbra region can provide neuroprotection after ischemia. Preconditioning exercise can reduce apoptotic activity in the penumbral region by enhancing the expression of neurotrophic factors such as MK and BDNF[16]. These factors promote neurite outgrowth and enhance neuronal activity[47,48], thereby providing a neuroprotective and regenerative role in cerebral ischemia. Heat shock protein (HSP-70) and ERK-mediated signal

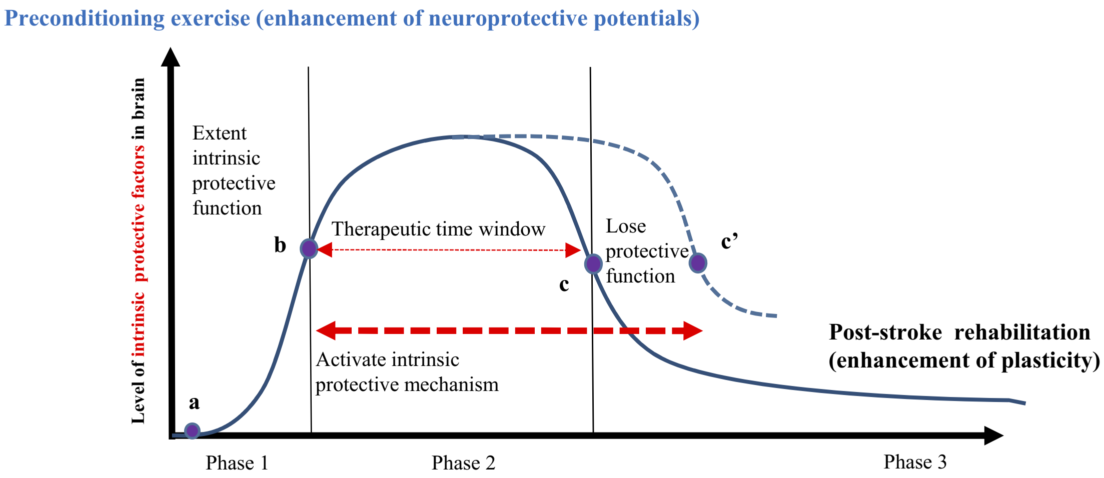

Figure 2. Schema of the time course of acute stroke. In the ischemic brain, neuroprotective factors increase during the early phase from a to b (phase 1). The level of protective factor expression peaks from b to c, the therapeutic time window (phase 2). Preconditioning exercise increases intrinsic protective factors in the penumbra region and may extend the therapeutic time window by enhancing the expression of intrinsic protective factors (from c to c'). During phase 3, the level of protective factor expression reduces. In this phase, post-stroke rehabilitation is important to enhance brain plasticity and functional recovery for stroke survivors.

pathways have been shown to be involved in ischemia-induced apoptosis[7]. Preconditioning exercise diminishes neuronal injury by upregulating HSP-70 and ERK1/2 in a rat model of stroke[30]. Moreover, exercise-induced neuroprotection is mediated by reduced MMP-9 expression in a rat stroke model[49,50]. Bcl-2 plays a pivotal role in the control of cell death and is upregulated by ischemic tolerance[51]. Our previous work demonstrated that preconditioning exercise exerts neuroprotective effects through the downregulation of the Bax/Bcl-2 ratio and caspase-3 activation after stroke[31]. Bcl-2 and Bax are anti- and pro-apoptotic proteins, respectively, while caspase-3 is activated in the apoptotic cell.

Preconditioning Exercise and Intrinsic Protective Factors

A number of intracellular intrinsic factors are present and can be activated to protect cells from injury, including cerebral ischemia[1]. Hypoxia-induced factor-1α (HIF-1α) is one of the most important transcriptional factors implicated in the hypoxic or ischemic brain and plays a key role in neuroprotection against ischemic brain injury[1,52]. In addition, 14-3-3γ is an isotype of the 14-3-3 protein family (β, η, γ, δ, τ, ζ, and ε) and is most abundantly found in the brain[1,53]. The γ member of the 14-3-3 family exerts pleiotropic effects during various physiological processes, such as cell proliferation and anti-apoptosis[54,55]. Our previous study demonstrated that preconditioning exercise activates HIF-1α and 14-3-3γ in neurons and astrocytes and subsequently induced neuron- and astrocyte-mediated brain tolerance[35]. The upregulated 14-3-3γ induced by preconditioning exercise reduces ischemic neuronal cell death through the 14-3-3γ/p-β-catenin Ser37/Bax/caspase 3 anti-apoptotic pathway after ischemic stroke in rats[35]. Understanding the mode of induction and mechanism of protection for these intrinsic protective factors would be beneficial for administering preconditioning exercise to extend the therapeutic time window, leading to better management of patients with stroke (Figure 2).

Preconditioning Exercise and Excitatory System

The excessive release of excitatory neurotransmitter glutamate after stroke leads to neuronal excitotoxicity and subsequent brain damage[13]. Preconditioning exercise reduces the overexpression of glutamate and its receptors, metabotropic glutamate receptor 5 (mGluR5) and N-methyl-D-aspartate receptor subunit type 2B (NR2B) in rat ischemic stroke models[56]. Another study showed that preconditioning exercise prior to ischemic reperfusion increased the antioxidant ability and decreased the oxidative damage in the rat brain[22]. Apoptosis and oxidative damage play critical roles following ischemic reperfusion injury. We have shown that preconditioning exercise after ischemic reperfusion reduces peroxynitrite-induced neurotoxicity in the brain[16], which suggests that preconditioning exercise decreases oxidative damage to the brain following ischemic reperfusion injury.

Preconditioning Exercise and Inflammatory Response

Brain ischemia induces a serious inflammatory response. Various inflammatory mediators such as TNF-α or IL-6 are released by ischemic brain cells; these mediators can exacerbate the deleterious effects of ischemic brain injury[57]. Preconditioning inhibits inflammatory injury by reducing the expression of inflammatory mediators as well as reducing the accumulation of leukocytes during reperfusion, thus leading to reduced brain damage[13]. Preconditioning exercise exerts neuroprotective effects through the regulation of the toll-like receptor (TLR) 4/nuclear factor-κB (NF-κB) signaling pathway and reduced inflammatory mediators (TNF-α or IL-1β) in the peripheral serum during ischemic reperfusion injury[24]. In summary, preconditioning exercise might ameliorate inflammatory responses by regulating inflammatory cascades in ischemic stroke.

Preconditioning Exercise and Clinical Application

Physical activity is one of the lifestyle factors that are associated with a reduced risk of stroke. Meta-analyses of the physical activity and stroke risk relationship have demonstrated that leisure-time physical activity reduces the risk of total, ischemic, and hemorrhagic stroke[58]. While many studies have investigated the association between physical activity and risk of stroke, few clinical studies have explored whether prestroke physical activity is associated with better functional outcome of stroke or stroke severity.

Retrospective studies have shown that patients with stroke who reported regular exercising before stroke onset have milder strokes and better functional outcomes after stroke[59-63]. In a retrospective clinical study of 673 patients with stroke, a high or moderate level of physical activity was associated with a high Barthel Index (BI) score at enrollment and 3-months follow-up as part of the Ischemic Stroke Genetics Study[61]. Another retrospective clinical study of 265 patients with stroke, which represents a subset of patients with first-time stroke enrolled in the ExStroke Pilot Trial, showed that physical activity prior to stroke was associated with a milder stroke and better long-term outcomes[60]. In a cross-sectional study of 362 patients with acute ischemic stroke admitted to the Stroke Unit of Lille University Hospital, less severe stroke was associated with the duration of weekly exercise prior to stroke using the National Institutes of Health Stroke Scale, modified Rankin scale (nRS), and BI, thus suggesting that physical activity is a simple way to decrease cerebral ischemia severity[63]. Taken together, these clinical studies suggest that prestroke physical activity decreases the severity of stroke and improves the subsequent functional outcome.

However, a large prospective cohort study enrolling healthy men without a history of stroke at baseline, showed little evidence that prestroke physical activity influences functional outcome after stroke[64]. In another prospective observational multicenter study conducted in French and Japanese patients with stroke treated with intravenous recombinant tissue plasminogen activator (rt-PA), prestroke physical activity had little or no influence on outcome 3 months after treatment for cerebral ischemia with rt-PA[65]. A prospective clinical study monitored 18,117 adults without a history of stroke for 12 years and reported that physical inactivity before stroke was associated with a higher risk of being dependent both before and after a stroke event[66]. These studies show that the beneficial effects of physical activity prior to stroke are controversial in clinical settings. A possible explanation for this discrepancy in study findings might be related to the different populations and design of studies. In addition, the molecular mechanism underling preconditioning exercise in stroke has not yet been explored in detail. In a review of exercise studies in elderly individuals, peripheral markers such as BDNF, IGF-1, and VEGF were potentially useful indicators of neuroplasticity[67]. However, additional longitudinal studies are required to examine the beneficial effects of physical activity prior to stroke.

As mentioned before, preconditioning using a preceding sublethal ischemic insult is an attractive strategy for protecting neurons by inducing ischemic tolerance in the brain. Physical exercise may be a promising preconditioning method to induce brain ischemic tolerance after stroke; however, some elderly patients are unable or unwilling to exercise after stroke. In such patients, remote ischemic conditioning (RIC) can be potentially effective in inducing neuroprotection in patients with a neuronal disorder. RIC triggers endogenous protective pathways in distant organs such as the heart and brain, thereby inducing neuroprotection. RIC involves the repetitive inflation and deflation of a blood pressure cuff on the limb; it has been shown to improve cerebral circulation in patients with symptomatic intracranial arterial stenosis and is a safe and effective therapy for elderly patients[68]. In addition, RIC is potentially effective in patients with cerebral small-vessel disease in slowing cognitive decline and reducing white matter hyperintensities[69]. It is a feasible therapeutic approach with good compliance for targeted population. The experimental evidence suggests that RIC and physical exercise share common mechanisms[70]; therefore, preconditioning exercise can be considered a form of remote conditioning, and conversely, RIC can be viewed as an equivalent to preconditioning exercise in patients unable or unwilling to exercise.

Conclusion

In conclusion, preconditioning exercise appears to induce brain ischemia tolerance and has been shown to exert beneficial effects in both preclinical and clinical studies. Elucidating the mechanisms of preconditioning exercise-induced neuroprotection after stroke will help in the development of new treatment strategies for patients with stroke.

Clinically, preconditioning exercise and remote preconditioning exercise are safe and feasible, thus representing an exciting new paradigm in endogenous neuroprotection for patients with acute and chronic stroke.

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Conflict of Interest: The author declares no conflicts of interest.

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