REVIEW ARTICLE

Neuroprotection of Early Locomotor Exercise Poststroke: Evidence From Animal Studies

Pengyue Zhang, Jia Xianglei, Yang Hongbo, Jichuan Zhang, Ce Xu

ABSTRACT: Early locomotor exercise after stroke has attracted a great deal of attention in clinical and animal research in recent years. A series of animal studies showed that early locomotor exercise poststroke could protect against ischemic brain injury and improve functional outcomes through the promotion of angiogenesis, inhibition of acute inflammatory response and neuron apoptosis, and protection of the blood-brain barrier. However, to date, the clinical application of early locomotor exercise poststroke was limited because some clinicians have little confidence in its effectiveness. Here we review the current progress of early locomotor exercise poststroke in animal models. We hope that a comprehensive awareness of the early locomotor exercise poststroke may help to implement early locomotor exercise more appropriately in treatment for ischemic stroke.

RÉSUMÉ: Neuroprotection conférée par l'exercice locomoteur précoce après un accident vasculaire cérébral : données tirées des études chez l'animal. L'exercice locomoteur précoce après un accident vasculaire cérébral (AVC) a retenu l'attention en recherche clinique et en recherche chez l'animal au cours des dernières années. Plusieurs études chez l'animal ont montré que l'exercice locomoteur précoce après un AVC protégerait contre une lésion ischémique du cerveau et pourrait améliorer l'issue fonctionnelle en favorisant l'angiogenèse, l'inhibition de la réponse inflammatoire aiguë et l'apoptose neuronale ainsi que la protection de la barrière hémato-encéphalique. Cependant, à ce jour, le recours en clinique à l'exercice locomoteur précoce après un AVC a été limité parce que certains cliniciens ont peu confiance en son efficacité. Nous revoyons les progrès actuels dans le domaine de l'exercice locomoteur précoce après un AVC chez des modèles animaux. Nous espérons qu'une sensibilisation à l'exercice locomoteur précoce après un AVC pourra favoriser une utilisation de l'exercice locomoteur précoce de façon plus appropriée dans le traitement de l'AVC ischémique.

Keywords: Cerebral ischemia, Early exercise, Mechanism of neuroprotection, Neuron apoptosis

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INTRODUCTION

Cerebral ischemia is one of the most serious neurological disorders and is the most common cause of permanent disability all over the world.[1] Its sequelae not only reduce the quality of survivor's life, but also put a heavy burden on families and society.[2] Although a great deal of effort have been made in past decades, today we still lack effective strategies that can improve functional outcome in stroke survivors.[3]

The early phase postischemia is the critical time window for the functional recovery in which plenty of neuroprotective mechanisms were initiated, such as neurogenesis, functional plasticity, axonal sprouting and synaptogenesis, and attenuation of muscle atrophy in unaffected sides.[4-6] This time window is sensitive to specific treatments that can trigger and promote neuroprotective mechanisms in spontaneous recovery.

In recent years, increasing clinic evidence has suggested that early locomotor exercise after stroke facilitated the functional recovery from stroke and had attracted a great deal of attention.[7] The benefits of early locomotor exercise after stroke included fewer deaths, fewer and less severe complications, less disability, and better quality of life.[8-10] Moreover, early locomotor exercise poststroke has currently been recommended in a range of clinical guidelines, such as the Clinical Guidelines for Stroke Management 2010 document sponsored by the National Stroke Foundation in Australia.[11] Although early locomotor exercise poststroke was considered an important and potential treatment strategy for stroke, its clinical application is limited. Some clinicians have little confidence in its effectiveness because of the absence of high-quality randomized, double-blind, control clinical trials and an undefined molecular mechanism.[12,13]

Although there are some differences between patient and animal models, the animal studies can help us explore underlying molecular mechanisms that is difficult to achieve in clinical trials. The unmasked mechanism may increase the willingness of clinicians to implement the early locomotor exercise poststroke in clinical settings. Here we review the mechanism of early locomotor exercise poststroke in animal stroke models in recent years. We hope that a comprehensive awareness of early

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Table 1: References of early exercise after stroke

Exercise protocol	Starting time	Functional performance	Molecular mechanism	References
Voluntarily exercise	24 hours	Positive	Decreased infarct volume; neuroplasticity	114,135
		Negative	Decreased neurogenesis in subventricular zone;	132
	48 hours	Positive	BDNF, NGF, GAP43, neuroplasticity	85,124,126,128
	72 hours	Positive	Apoptosis, angiogenesis	71,111,136
Constant force exercise	24 hours	Positive	Neuroplasticity; BDNF, anti-neuroinflammation, insulin-like growth factor I signaling; neuroplasticity, angiogenesis, neurogenesis	18,20,25,28,29,30,48,75,87,90,91,115,125,127
	48 hours	Positive	Attenuating muscle atrophy	6,148
	72 hours	Positive	Anti-neuroinflammation, angiogenesis, neurogenesis	57,72,110,134
Gradually increased force exercise	24 hours	Positive	Anti-neuroinflammation, apoptosis, angiogenesis, NGF, netrin-1, blood-brain barrier, BDNF, neurogenesis, mitochondrial biogenesis	16,17,19,28,49,74,82,83,112,113,116,130,144,145
	48 hours	Positive	Apoptosis, neurogenesis, neurotrophin 4	73,89
	72 hours	Positive	Neuroplasticity	129
Compared between voluntary and force exercise	24 hours	Positive	BDNF	84,86

NGF, nerve growth factors.

locomotor exercise may help implement early locomotor exercise more appropriately in treatment for cerebral ischemic stroke.

Search Methodology and Results

We aimed to identify all rodent animal studies relating to cerebral ischemia, early locomotor exercise poststroke, behavioral recovery, and mechanism. We searched PubMed including all years up to January 2015 (English language only). We included animal studies that used global or focal ischemic stroke. Any intervention using early locomotor exercise, such as forced or voluntary locomotor exercise, was included.

Based on the keywords "cerebral ischemia" and "exercise," we obtained 826 titles. Of these, 258 studies were animal models and their abstracts were identified for further review. Reference lists in these articles were hand-searched for further studies with potential relevance. Finally, 49 studies met the criteria (rodent model, cerebral ischemia, early-initiated [24-72 hours poststroke], and locomotor exercise intervention) and measured the effects of early locomotor exercise postcerebral ischemia on brain repair and so were included in this review (Table 1).

Definition of Early Locomotor Exercise

To implement early locomotor exercise appropriately, it is crucial to define the time window of the early phase after stroke. However, there is not a standard definition of early phase either in clinical applications or animal studies. In the clinical setting, 24 hours, the first 3 days, and the first week after stroke onset were considered as early phase.[14,15] The time window is one of the direct guides for clinical therapy. However, the optimal time point for early exercise depends on multiple factors including race, sex, age, lifestyle, complications, and individual differences. Thus the early phase after stroke cannot be defined only by time point in the clinical setting.

This issue becomes simple in animal model because we can control almost all conditions in experiments including the type of animal, sex, age, and severity of stroke. The middle cerebral artery occlusion is widely used in rodent stroke model. In most reports, early exercise was initiated during 24 to 72 hours after middle cerebral artery occlusion in rodents with 60 to 120 minutes of ischemia[16-20] (Table 1). Thus the exercise begun 24 to 72 hours after stroke was defined as early exercise in this review, with the training period lasting from 1 to 4 weeks.

The locomotor exercise program in this review included voluntary exercise and forced exercise (constant intensity during all training periods and gradually increased intensity during the first few days) (Table 1).

Histological and Functional Improvement

The death of neurons is the disastrous consequence of cerebral ischemia, which leads to serious histological damages and the formation of an infarct zone in brain parenchyma. The neurons in the ischemic core die via irreversible necrosis and apoptosis. Subsequently, most cells in the penumbra, region that surrounds the infarct zone, undergo apoptosis gradually after stroke.[21] These cells can potentially be rescued in the early phase of cerebral ischemia by inhibiting the apoptotic pathway or by recovering the cerebral blood. Because decreased neuron death means reduced infarct volume and promoted functional recovery, the treatment strategies to date that could reduce infarct volume are potential protocols in stroke treatment.

Locomotor exercise at early phase is one kind of treatment in after-stroke recovery. However, early locomotor exercise did not reduce infarct volume consequentially; the infarct volume in ischemic rats may even be enlarged by conditioned overuse of the affected limb and high-intensity exercise at early phase after stroke.[22-24] Early locomotor exercise with a proper intensity

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reduced the infarct volume.[25] Although early locomotor exercise significantly promoted motor coordination and alleviated neurological deficits,[25,26] the promoted functional recovery is not accompanied by reduced infarct volume.[27] Furthermore, the effect of early locomotor exercise on recovery is timing window–dependent. Yang[28] and Rasmus et al[29] demonstrated that rats with one week of mild treadmill training initiated 24 hours after operation had reduced infarct volume and better functional recovery than rats with equal training initiated one week after operation. Our group also demonstrated that early treadmill training with gradually increased intensity significantly reduced infarct volume and promoted functional recovery of motor and memory. Moreover, aging is often accompanied by stroke attack. Two weeks of early locomotor exercise decreased the infarct volume both in young and old rats compared with the control group, but the young rats had a smaller infarct volume than did the older rats.[30]

In summary, these experimental studies indicate that locomotor exercise with mild to moderate intensity initiated early may decrease histological damage and enhance functional recovery from cerebral ischemia.

Neuroprotective Mechanism of Early Exercise

Early locomotor exercise initiates multiple neuroprotective responses in injured brains such as change of cerebral blood flow, gene expression, angiogenesis, neurogenesis, mitochondrial biogenesis, suppression of apoptosis, and neuroinflammation response. Their synergistic effect contributes to neuroprotection and subsequent functional recovery (Table 1).

Early Locomotor Exercise Attenuates Neuroinflammation Response

Cerebral ischemia is accompanied with the inflammatory responses, such as the production of proinflammatory cytokines, chemokines, and adhesion molecules and activation of the resident glial cells. These processes start within hours after ischemia and persist for months.[31,32] Although inflammatory responses exerted some beneficial effects in recovery from stroke,[33-35] accumulating evidence showed that inflammatory response in the acute ischemic period was one of the main factors that led to brain damage and exacerbated ischemic injury in potentially viable tissues through secretion of deleterious molecules, such as glutamate, and production of reactive oxygen species and nitric oxide.[36-40] Some experimental evidence have demonstrated that inhibition of acute inflammatory responses with antagonists, neutralizing antibodies, or gene knockouts relieved the detrimental effects and markedly improved functional recovery.[41,42]

Existing evidence shows that physical exercise diminishes inflammation in some chronic diseases and in aged mice.[43] The molecular mechanism involves the reduction of macrophage infiltration, expression of inducible nitric oxide synthase and tumor necrosis factor-alpha in the heart and expression of chemokines and cytokines in the circulatory system.[44-46] Interestingly, a recent article has indicated that preischemic physical exercise led to chronically increased expression of tumor necrosis factor-alpha during exercise, which conversely ameliorated inflammatory injury induced by ischemia/reperfusion.[47] A possible explanation is that the chronically proinflammatory response during exercise led to ischemic tolerance, a phenomenon in which minor injury before ischemia led to a greater tolerance to subsequent serious injury. Recent research has focused on the effect of postischemic physical exercise on the acute inflammatory response. Our data indicated that early locomotor exercise after stroke significantly attenuated the acute neuroinflammation through decreasing proinflammatory cytokines and cell adhesion molecules, suppressing the activation of astrocytosis and microglia, and attenuating the detriment of over-released glutamate.[19,48] Furthermore, we found that early locomotor exercise protects blood-brain barrier (BBB) integrity against ischemia/refusion injury.[49] The disrupted BBB is a critical early event that initiates the inflammatory cascade and exaggerates edema, which ultimately results in poor outcomes.[50] Recent studies have indicated Toll-like receptor (TLR) signaling pathways are also involved the neuroprotective action of early locomotor exercise. TLRs are a group of important receptors in the brain's innate immune system; they play a critical role in initiating and modulating the inflammatory cascade caused by cerebral ischemia through recruiting and linking to their endogenous ligands released from damaged neuronal cells.[51-53] Studies have shown that early locomotor exercise decreased TLR expression on cell-surface and inflammatory cytokine production in monocytes in ischemic brain tissue.[54-56] The main downstream targets of TLR2/4, MyD88, and nuclear factor-κB were also reduced by early exercise following cerebral ischemia.[57] In summary, early locomotor exercise after stroke may attenuate acute inflammatory responses via reduced expression of proinflammatory cytokines and inhibited BBB dysfunction so as to confer neuroprotective action.

Early Locomotor Exercise Suppresses Neural Apoptosis in Penumbra

Cerebral ischemia leads to irreversible death of neurons in the ischemic core. However, some neurons in penumbra survive with dysfunction and then undergo apoptosis if they do not receive effective therapeutic treatment.[58-60] Thus, these injured neurons could be rescued in early-phase postischemia, and suppression of apoptosis may potentially be an opportunity to salvage these neurons and then alleviate brain injury.[61,62] Increasing evidence shows that appropriate locomotor exercise could suppress apoptosis in many diseases,[63,64] particularly in ischemic myocardial infarction[65,66] and Alzheimer disease[67] by reducing the expression of proapoptotic proteins and increasing the expression of antiapoptotic proteins.[68-70] Two-week early locomotor exercise started at 48 or 72 hours poststroke significantly reduces the number of TdT-mediated dUTP-biotin nick-end labeling–positive cells and suppressed autophagosomes.[71-73] Even early locomotor exercise started at 24 hours after stroke also significantly improves neurological function by decreasing caspase-3 and cleaved caspase-3 expression and the number of apoptotic cells detected by Fluoro-Jade-B staining and TdT-mediated dUTP-biotin nick-end labeling concurrently by increasing Bcl-2 (a key antiapoptotic protein) expression detected by western blotting.[16,74,75] These results indicate that suppressing neural apoptosis in the penumbra may be the potential underlying mechanism conferred to the neuroprotective mechanism induced by early locomotor exercise following cerebral ischemia.

Early Locomotor Exercise Increases Expression of Neurotrophic Factors

Neurotrophic factors play crucial roles in neuronal survival, repair, and recovery from stroke.[76] However, their clinical

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application is limited because the recombinant neurotrophic factors cannot cross the BBB.[77] It is well-known that exercise can upregulate the expression of nerve growth factors in rats with both normal and diseased brains, such as brain-derived neurotrophic factor (BDNF),[78-81] nerve growth factors, and neurotrophin, and so on.

Similarly, recent reports indicate that early locomotor exercise following stroke increases the expression of neurotrophic factors, such as BDNF and insulin-like growth factor (IGF), the possible mechanisms involved in the 5-HT, Trk, and AKT signaling pathways.[82-87] The increased BDNF induced by early locomotor exercise is mainly distributed in the contralateral hemisphere and the penumbra in the ipsilateral hemisphere.[88] The expression levels of nerve growth factors and Midkine are significantly upregulated in the cells around the infarct zone of the ischemic rats that received low-intensity early locomotor exercise compared with the ischemia-only sedentary rats.[17] Early locomotor exercise increases neurotrophin-4 protein level in the bilateral hemispheres compared with the ischemia-only sedentary rats, particularly in the contralateral hemisphere and the zone that adjacent to the ischemic region; this increase was detected as early as day 9 after ischemia.[89] The study by Chang et al found that early locomotor exercise increases the IGF-I concentration through promoted IGF-I entrance into the affected brain zone and increased its expression. Inhibiting IGF-I signaling eliminates such protective effects.[90] A study conducted by Ohwatashi et al found that early locomotor exercise induces increased expression of glial cell line-derived neurotrophic factor in rats who underwent photochemical infarction.[91] It is noteworthy that Liu et al[82] demonstrated that early locomotor exercise started at 24 hours significantly increased the expression of netrin-1 and its receptors, which regulate diverse recovery processes including neuron survival and migration,[92,93] axonal outgrowth and branching,[94] and angiogenesis.[95]

Early Locomotor Exercise Enhances the Angiogenesis and Improves Cerebral Blood Flow in the Ischemic Zone

Angiogenesis is a neuroprotective response induced by hypoxia within a few hours after the onset of stroke. The expression of a group of angiogenic factors including vascular endothelial growth factor, Ang1/2, and their receptor Tie2 in infarct hemisphere was gradually upregulated for weeks after stroke. These proteins trigger the proliferation of endothelial cells and neovascularization.[96-99] Krupinski et al found some vascular buds and connections in an ischemic rat by brain vascular cast method.[100] Newly formatted blood vessels not only improve the exchange of oxygen and glucose through increased blood flow,[101,102] but also remove damaged tissues and ameliorate the microenvironment in hypoxic tissue.[103] The improved microenvironment rescues the injured neurons and promotes the proliferation and migration of neural stem cells.[104,105] Indeed, clinical observation found that stroke patients with more newly formatted blood vessels survive a longer time.[106,107] Thus, improving angiogenesis after stroke plays a crucial role in recovery from stroke and is a potential strategy for treatment of ischemia.[108,109]

Early locomotor exercise after ischemia has been shown to augment angiogenesis through increasing the messenger RNA transcription and protein translation of angiopoietins, such as vascular endothelial growth factor[110], PECAM-1[72], CD31[111], Ang1, and their receptor Tie2.[112,113] Endothelial nitric oxide synthesis may be an underlying mechanism because the lack of endothelial nitric oxide synthase abolishes the beneficial effects of early locomotor exercise on angiogenesis.[114] Recently, we demonstrated that these newly formatted vessels increased by early locomotor exercise indeed give rise to new functional vessels and improve the cerebral blood flow in ischemic brain zone visualized by laser speckle flowmetry, a noninvasive imaging blood flow technique.[112] The similar result was achieved in Yang's study, which reported increased CD31-positive blood vessel density in the affected striatum.[115] Furthermore, an in vitro study indicated that a modest flow induced by appropriate locomotor exercise decreases brain microvascular endothelial cells apoptosis in the ischemic condition.[116] These results suggested that early locomotor exercise can improve cerebral blood flow through angiogenesis and increase blood flow rate in the ischemic brain zone.

Early Locomotor Exercise Promotes Neuroplasticity: Neurogenesis and Synaptic Reorganization

Neuroplasticity is a critical element in brain repair after stroke. Accumulative evidence has suggested that some newborn neurons after stroke were functionally recruited and formed appropriate synapses with the existing neurons in hippocampus.[117-119] In addition to neurogenesis, synaptic reorganization is another key constituent in functional recovery following stroke.[120] The neurons in peri-infarct region of ipsilateral hemisphere and the contralateral hemisphere form some new synapses with survived neurons and newborn neurons.[121]

There is increasing evidence to show that locomotor exercise promoted neuroplasticity both in normal and ischemic animals.[76,122] Several reports have shown that locomotor exercise initiated within 7 days after stroke enhances neurogenesis and functional recovery.[123] Some recent studies have detected the change of protein expression profile induced by early locomotor exercise in the cortex of rats with stroke. These results suggest that early locomotor exercise after stroke upregulate a group of proteins that promote synaptic plasticity, such as growth-associated protein 43 (GAP43, the key axon growth-associated protein), Syn1, synaptosomal-associated protein (SNAP-25), PSD95, and others.[124-129] Accordingly, increased neurogenesis was detected in the hippocampus dentate gyrus and peri-infarct regions in rats who underwent early locomotor exercise.[130] During spontaneous recovery after ischemia, many of these newborn neurons undergo apoptosis,[131] but early locomotor exercise significantly increases the neurogenesis and decreases the number of apoptotic cells.[71] However, some reports show that early locomotor exercise poststroke reduces neurogenesis in the subventricular zone and dentate gyrus.[132-134] These inconsistent results could be due to different models and exercise protocols used. Ameliorative neuroplasticity can be detected by electrophysiology. The results from Tang et al[135,136] indicate that early locomotor exercise enhanced activity-dependent long-term depression through PICK1-dependent mechanisms and an increased expression level of AMPA receptor subunits that can increase synaptic transmission. Thus early locomotor exercise postischemia promotes neuroplasticity through neurogenesis and synaptogenesis and increases the functional synapse.

Early Locomotor Exercise Promotes Mitochondrial Biogenesis

Mitochondria is a critical organelle that supports the neuronal survival, metabolism, synthesis, and release of neurotransmitters

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and recovery from injury.[137,138] However, mitochondrion play opposite roles during cerebral ischemic injury. On the one hand, injured mitochondria releases a great deal of reactive oxygen species that initiate detrimental cascade; on the other hand, biogenesis of functional mitochondria induced by stroke is helpful for neuroprotection and recovery.[137,139] Thus, the strategy to decrease mitochondria damage and increase mitochondrial biogenesis would be important to neuroprotective treatment after stroke.[140] Consistent evidence suggests that exercise increases mitochondrial biogenesis in healthy and ischemic brains.[141-143] Recent evidence from our laboratory shows that early locomotor exercise started 24 hours after stroke increases mitochondrial DNA content and significantly enhances the messenger RNA and protein expression of three transcription factors considered critical for mitochondrial gene transcription and DNA replication: PGC-1, NRF-1, and TFAM.[144,145] These results indicate that early locomotor exercise after stroke could enhance mitochondrial biogenesis and may serve as a key component of early locomotor exercise–induced neuroprotective mechanisms in the ischemic brain.

Summary and Prospects

Locomotor exercise is an effective, inexpensive, home-based, and accessible intervention strategy. Early locomotor exercise poststroke has attracted a great deal of attention in rehabilitative centers and laboratories. Animal studies have increasingly revealed that early locomotor exercise induced neuroprotective mechanisms in the ischemic brain; randomized control trials with larger sample number are further exploring the optimal early locomotor exercise protocol. This evidence from clinical and animal studies indicates that early locomotor exercise poststroke was beneficial for recovery from cerebral ischemia and that it can be applied safely. However, to apply early locomotor exercise in clinical practice and maximize functional outcome, the choice of interventional protocol should be considered carefully. The first consideration is how to choose the type of locomotor exercise. Cumulative evidence indicates that different exercise protocols could lead to an entirely different outcome.[84,86,115] There are many locomotor exercise manipulations that could be used conveniently, but so far this is no unified standard to assist in choosing the optimum type. The second consideration is whether early locomotor exercise combined with other rehabilitative treatments or drugs is more reasonable than locomotor exercise only.[146,147] A related rehabilitative treatment may be functional electrical stimulation, acupuncture, music stimulus, light stimulus, skilled training, and so on. Drugs can include multiple agents that alleviate inflammatory response and neuronal apoptosis and promote angiogenesis and neurogenesis. Additionally, some locomotor exercise can be carried out under the help of body-weight support or a robot.[148] The third consideration is how we can determine the amount and intensity of early locomotor exercise based on different levels of severity in a stroke patient. According to our knowledge from animal studies and clinic observations, low and gradually increased exercise intensity should be performed in the early phase after stroke.[20,125,149]

In summary, early exercise poststroke was safe, feasible, and effective (Table 1). But its implementation in a clinical setting should be cautiously introduced and based on each individual's condition.

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