Life Sciences 198 (2018) 32–37

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

The beneficial role of early exercise training following stroke and possible mechanisms

Ying Xing[a], Si-Dong Yang[b], Fang Dong[c], Man-Man Wang[a], Ya-Shuo Feng[a], Feng Zhang[a,d,*]

[a] Department of Rehabilitation Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[b] Department of Spine Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[c] Department of Clinical Laboratory Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[d] Hebei Provincial Orthopedic Biomechanics Key Laboratory, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China

ARTICLE INFO

Keywords:
Exercise
Ischemic stroke
Neuroprotection

ABSTRACT

Exercise training is a regular therapy for stroke patients in clinic. However, whether the early exercise is beneficial for stroke patients is still controversial. The review was performed in databases of OVID, PUBMED, and ISI Web of Science, from respective inception to December 2017. In this review, we summarize the effect of different exercise intensity, initiation time, and style on ischemic stroke. Moreover, the possible mechanism is also discussed. The conclusion is that the voluntary exercise is better in promoting the functional recovery following stroke compared to forced exercise; too early initiated exercise might play a harmful role following stroke, while early initiated exercise might exert benefits after stroke; mild and moderate intensity exercise training could generate better neuroprotection in comparison with high intensity exercise training; early excise training could regulate the process of brain edema, cell apoptosis, oxidative damage, stem cells and other mechanisms in order to exert neuroprotection for brain.

1. Introduction

Stroke is the third main cause of death resulting from cardiovascular disease and cancer in majority of the developed countries [1]. Studies have indicated that 20% of stroke survivors need medical institutional care 3 months after stroke, and almostly15–30% of stroke survivors suffer from long-term disability [2]. The major pathological mechanisms of ischemic brain damage embrace inflammatory reaction, oxidative activation, protease activation, intracellular excitatory toxicity and disruption of Ca^{2+} homeostasis [3]. Except for thrombolysis, which is restricted by a narrow remedial window, there is no effective therapy proven to facilitate neurological rehabilitation in the phase of post-stroke [4]. Exercise training enhances motor function and cognitive ability which is involved in formation of memory and learning following ischemia [5]. Among several exercise paradigms, the common exercise models included forced treadmill training, voluntary wheel training, and involuntary muscle contraction induced by electrical stimulation [6]. These exercises have been proved to enhance cognitive function and promote neural rehabilitation as well as physical benefits following brain injury [6]. In addition, Aidar et al. demonstrates that resistance exercise training may improve state and trait anxiety in persons who suffered from minor to moderately severe function deficit more than one year following stroke [7]. Li et al. highlights that the exercise timing is important in rehabilitation process from physical disability and injury after stroke [8]. In animal models after stroke, a series of studies have demonstrated benefits via exercise intervention if started during the early phase (24 h) following ischemic or hemorrhagic stroke [9,10,11]. In contrary, Risedal et al. indicates that initiation of exercise training within 24 h following permanent focal cerebral ischemia can aggravate cortical tissue injury [12]. Thus, our aim in this review was to discuss the influence of early exercise on post-ischemic rehabilitation and others influence factors in the early stage after ischemic stroke.

2. The key role of exercise initiation time following stroke

2.1. Clinical studies

Morreale et al. report that a time-dependent rehabilitative effect may exist in the process of motor recovery after stroke, especially for lower extremity improvement [13]. Very early mobilization initiated within 24 h following stroke seems viable and safe for acute-stroke patients [14].

* Corresponding author at: Department of Rehabilitation Medicine, The Third Hospital of Hebei Medical University, No. 139 Ziqiang Road, 050051 Shijiazhuang, Hebei, PR China.
E-mail address: zjk20019@126.com (F. Zhang).

https://doi.org/10.1016/j.lfs.2018.02.018
Received 18 January 2018; Received in revised form 4 February 2018; Accepted 12 February 2018
Available online 13 February 2018
0024-3205/

2.2. Experimental studies

Nielsen et al. demonstrate that initiation of rehabilitative training in a proper phase after stroke may induce better effects and is possibly associated with a better function recovery [15]. The passive movement may improve the memory function and learning ability in cerebral ischemic rats, which is partly caused by the inhibition of neural apoptosis, and at 24 h following ischemic stroke is the ideal therapeutic time compared to at 6,12,48,72 h [16] Buiatti et al. show that treadmill training may prompt motor behavior recovery following ischemic stroke, except when it initiates 12 h following surgery [17].

Rehabilitative training after ischemic stroke may rapidly improve movement quality and motor performance. While, early motor exercise (post-stroke 18 day) following stroke may contribute to produce the evolvement of post-ischemia neural network [18]. Risedal et al. suggest that exercise started 24 h following permanent focal cerebral ischemia may aggravate cortical tissue damage [12]. Exercise training may improve cerebral blood flow by enhancement of endothelium-dependent laminar shear stress, alleviating cerebral microvascular endothelial cell apoptosis in rat, which may be one of the possible protective mechanisms of very early started physical training (within 24 h post-stroke) [19]. Zhang et al. suggest that early locomotor initiated during 24 to 72 h following stroke may increase mitochondrial biogenesis, which might play an important role in the mechanisms of early locomotor exercise-caused neuroprotection in the ischemic brain [20].

Very early physical rehabilitation within 24 h post-stroke may provide notable neuroprotection against ischemic stroke injury via reducing cerebral edema, pro-inflammatory reactions, BBB dysfunction, and behavioral and cognitive damage [21]. Zhang et al. show that neuron apoptosis could be alleviated by early exercise initiated at 24 h post-ischemia via inhibiting neuron cell apoptosis [10]. Li et al. show that very early(within 6 h) and early(within 24 h) exercise following stroke increase generation of cell stress related factors(HIF-α and Hsp70), cell adhesion molecules (VCAM-1 and ICAM-1), and pro-inflammatory markers (TNF-αand IL-β), while late(3 days) exercise following stroke lessens expression level of above mentioned molecules [22]. Very early stage exercise following stroke may lead to elevated generation of pro-inflammatory cytokines, and up-regulated expression of cell stress, which may aggravate the tissue injury induced by brain ischemia/reperfusion damage [22]. Nitric oxide synthase (NOX) activation and Hyperglycolysis were involved in a promotion of cell apoptosis following exercise training in very early stage, and the exercise-induced adverse effect on stroke rehabilitation became weak while exercise was started 24 h following reperfusion [23]. Li et al. show that very early exercise started within 6 h following cerebral ischemia activates generation of proapoptotic factors for instance caspase-3 and BAX, which might be related to cell apoptosis [24].

The intervention initiation time between 24 h to 3 days following stroke may enhance exercise's beneficial effects and avert underlying detrimental effect which might hinder better functional outcome [24]. Early aerobic exercise training started at 72 h after surgery may alleviate neuronal death, reduce motor dysfunction, and inhibit the activation of astrocytes and microglial cells. Moreover, early aerobic training decrease the generation of the chemokine monocyte chemotactic protein-1 and cytokine interleukin-1β in transient MCAO rats [25]. Early exercise training started at 24 h after ischemia was more effective in facilitating neural function recovery and mitigating cerebral infarct volume in comparison with spontaneous recovery [26]. The training exercise started 24 h following focal cerebral ischemia for 1 week can obviously prompt neurologic function and mitigate infarct volume, whereas training exercise started 1 week following focal cerebral ischemia cannot obviously exert beneficial effects compared with 2 week without training group [26]. Yang et al. demonstrates that early moderate exercise initiated at 24 h after ischemic stroke can obviously promote spatial memory and motor recovery, but not the balance and sense functions [27].

In summary, too early initiated exercise (less than 24 h following stroke) might play a harmful role following stroke, while early initiated exercise (24 to 72 h following stroke) might exert benefits after stroke. Therefore, the initiation time of exercise is a crucial factor to determine the good or bad effect following stroke.

3. The role of exercise style on function recovery following stroke

3.1. Active vs passive or voluntary vs forced exercise

3.1.1. Clinical studies

Bilateral initiating with both active and passive training may accelerate upper extremity functional rehabilitation in the early stage following stroke [28]. Silver et al. show that treadmill training prompt functional overground mobility in chronic stroke patients with stable hemiparesis [29]. Forced aerobic exercise may serve as a viable and safe recovery intervention to promote rehabilitation of motor and nonmotor function and to improve aerobic fitness in chronic stroke patients [30]. Platz et al. show that specificity of active exercise training seemed more crucial for motor function recovery in comparison with intensity (treatment time), and the motor function recovery in patients with mild or severe upper limb paresis may be accelerated by the compositive modular injury-oriented training method [31].

3.1.2. Experimental studies

In comparison with involuntary and forced exercises, voluntary exercise intervention shows a best beneficial effects in improvement of motor rehabilitation and enhancement of the hippocampal BDNF expression following cerebral ischemic stroke [32]. Ke et al. indicate that voluntary exercise intervention is very effective in prompting motor functional recovery and elevating the hippocampal BDNF expression, as well as reducing corticosterone stress response than involuntary and forced exercise group. But the forced exercise intervention shows low level of brain BDNF expression, less motor functional recovery and high corticosterone stress response [32]. Li et al. demonstrate that passive movement may improve the memory function and learning ability in cerebral ischemic rats, which is partly caused by the inhibition of neural apoptosis, and at 24 h following ischemic stroke is the ideal therapeutic time compared to at 6,12,48,72 h [16]. Marin et al. demonstrates that different from behavioral outcomes, no obvious impact was detected in histological and physiological outcomes following applying voluntary exercise 24 h following lesion maturation and the effect of exercise in MCAO rat can be concealed by repetitive outcomes testing [33]. Willed movement intervention may up-regulate the levels of growth-associated protein 43 and neurotrophin 3 in rats with cerebral ischemia/reperfusion injury, which might be associated with neuronal regeneration and repair [34].

3.2. Endurance exercise

3.2.1. Clinical studies

Ploughman et al. demonstrate that endurance exercise on a motorized running wheel prompts learning of subsequent challenging reaching tasks following stroke, which maybe optimize outcomes in stroke patients [35]. Endurance training on a motorized running wheel may facilitate the brain for learning of subsequent tasks in post-stroke patients. The potential mechanisms, although unknown, maybe result from activating noradrenergic systems involved in improved task vigilance and increase of neurotrophic factors for example BDNF [35]. Mild treadmill endurance training for six months leads to progressive and obvious decline in the cardiovascular needs and energy consumption of walking in aged patients with chronic stroke [36]. A rationale for endurance training is that exercise ability is determined by general fatigue rather than the hemiparetic limb for stroke patients [37].