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REVIEW

PHYSICAL EXERCISE TRAINING AND NEUROVASCULAR UNIT IN ISCHEMIC STROKE

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Abstract—Physical exercise could exert a neuroprotective effect in both clinical studies and animal experiments. A series of related studies have indicated that physical exercise could reduce infarct volume, alleviate neurological deficits, decrease blood–brain barrier dysfunction, promote angiogenesis in cerebral vascular and increase the survival rate after ischemic stroke. In this review, we summarized the protective effects of physical exercise on neurovascular unit (NVU), including neurons, astrocytes, pericytes and the extracellular matrix. Furthermore, it was demonstrated that exercise training could decrease the blood–brain barrier dysfunction and promote angiogenesis in cerebral vascular. An awareness of the exercise intervention benefits pre- and post stroke may lead more stroke patients and people with high-risk factors to accept exercise therapy for the prevention and treatment of stroke. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: neurovascular unit (NVU), stroke, angiogenesis, blood-brain barrier (BBB), cerebral blood vessels.

Contents

INTRODUCTION

In the preliminary stage of stroke research, researchers primarily focused on the biochemical events which were caused by the interruption of substrate delivery to neurons: ATP loss resulting in anoxic depolarization of neurons, and even necrosis. With the development of research methods, the focus changed to disorders of ion homeostasis, calcium ion overload and excitotoxicity, induction of reactive peroxide, resulting in membrane damage, mitochondrial and DNA injury, inflammation, and programed cell death (Dirnagl et al., 1999). The above-mentioned concepts mainly focused on neurons without supporting cells. However, the following studies indicated that the cells which interacted and supported neurons were equally damaged by ischemic stroke, and the supporting cells were also involved in crucial and complex cell-specific signaling pathways and execution cascades (Moskowitz et al., 2010).

In recent years, the concept of neurovascular unit (NVU) began to attract more and more attention in the research area of ischemic stroke. It was well-established that the NVU was essential for protecting neurons, maintaining the CNS homeostasis and coordinating the neuronal activity with supporting cells (Hawkins and Davis, 2005). The NVU emphasized the dynamic interaction among neurons, astrocytes, pericytes and extracellular matrix, including endothelial cells (EC) ensheathed with a basal lamina, smooth muscle cells, and so on, which played a key role in the pathobiology

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Abbreviations: AMPK, AMP- activated protein kinase; Ang-1, angiopoietin-1; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CFB, cerebral blood flow; EC, endothelial cells; ERK1/2, event-related kinase 1/2; IL-1β, interleukin-1β; GFAP, glial fibrillary acidic protein; GLT, glutamate transporter; GLUTs, glucose transporters; MMP, metalloproteinase; NGF, nerve growth factor; NVU, neurovascular unit; OGD, oxygen/glucose deprivation; p-Akt, phosphorylated Akt; PFK, phosphofructokinase; TJs, tight junctions; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

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of stroke (del Zoppo, 2009). The main function of the NVU was to control the passage of plasma components and cellular elements from the vessel blood into the brain (Rieckmann and Engelhardt, 2003). This barrier function, which was also known as the blood–brain barrier (BBB), was dependent on both the integrity of the endothelium and a functional interaction among EC, the basal lamina, and perivascular astrocytes (PA) (Hawkins and Davis, 2005).

Ischemic stroke is a main cause of death and disability worldwide. r(Goldstein et al., 2011). According to the previous studies, animal experiments demonstrated that physical exercise could reduce brain damage after ischemic stroke by increasing the survival rate, alleviating neurological deficits, mitigating BBB dysfunction and promoting neurovascular integrity (Ang et al., 2003; Endres et al., 2003; Li et al., 2004; Ding et al., 2006a; Tahamtan et al., 2013; Zhang et al., 2013a).

In clinical trials, physical exercise was reported to alleviate abnormal arterial blood pressure, decrease obesity, ameliorate glucose and lipid metabolic disorders and reduce the abnormal rheological properties of blood (Lee et al., 2003; Chrysohoou et al., 2005; Vinereanu, 2006). Moreover, it was well established that physical exercise could promote endothelial function, partly by activation of endothelial nitric oxide synthase (eNOS) (Chrysohoou et al., 2005) and extracellular superoxide dismutase (ecSOD). Other benefits of physical exercise were to reduce fibrinolysis, blood viscosity (Alevizos et al., 2005) and plasma fibrinogen concentration, promote HDL-cholesterol and increase plasma tissue plasminogen activator activity (Evenson et al., 1999).

VOLUNTARY AND FORCED EXERCISE IN ANIMAL EXPERIMENTS

In animal experiments, there were two kinds of exercise interventions: voluntary and forced (Hu et al., 2010b; Zhang et al., 2010b). Voluntary exercise allowed the animals to do exercise at will, imitating human daily activity or manual labor (Cotman and Berchtold, 2002). In contrast, forced exercise required that the animals did exercises on a treadmill for 20–30 min per day five to seven times per week (Ding et al., 2006b). Forced exercise could be deemed as the mimic of gym exercise as athletes. Although the two kinds of exercise manipulations were different in physical activity amount and time, they both could exert neuroprotective effects. Moreover, it was proved that forced exercise was better able to reduce infarct volume compared to voluntary exercise (Hayes et al., 2008).

EXERCISE TIMING NECESSARY TO INDUCE NEUROPROTECTION

As for the time span of exercise training which could exert neuroprotection for ischemic stroke, a previous study indicated that at least 2 weeks of treadmill training could ameliorate brain edema and decrease infarction size following ischemic stroke (Wang et al., 2001). Similarly, our previous study showed that 2 weeks and 4 weeks of exercise preconditioning could alleviate the over-release of glutamate and reduce brain damage following ischemic stroke, while 1 week of exercise preconditioning did not exert such protective effects (Jia et al., 2009). However, other studies reported that at least 3 weeks of treadmill training was required for inducing neuroprotection (Liebelt et al., 2010; Dornbos and Ding, 2012). Based on the above results, we could summarize that at least 2 or 3 weeks of pre-ischemic exercise training was necessary to exert neuroprotection after ischemic stroke. As for the exercise post-conditioning, several studies showed that at least 1 week of physical exercise could alleviate neurological deficits after ischemic stroke (Park et al., 2013; Zhang et al., 2013a). Moreover, other studies showed that post-ischemic exercise could alleviate neurological deficits or infarct volume at 3 or 4 days after ischemic stroke (Zhang et al., 2012a; Li et al., 2013). On the basis of the above results, we could conclude that at least 3 or 4 days of post-ischemic exercise training was required to exert neuroprotection after ischemic stroke.

PHYSICAL EXERCISE DECREASED NEURON DAMAGES IN ISCHEMIC STROKE

It was well established that stroke could cause a series of pathophysiological changes of neurons, even could cause neuron death, including apoptosis and necrosis. The intervention which could reduce neuron death was supposed to exert neuroprotection for brain tissues. A series of literatures demonstrated that physical exercise could maintain the number of viable cells in the hippocampus after the ischemic event, mitigate neuronal apoptosis, and enhance neuronal plasticity (Lan et al., 2013; Tahamtan et al., 2013; Zhang et al., 2013a). There were a variety of factors involved in the neuroprotective effect of physical exercise on neurons, including inflammatory response, calcium overload, neurons metabolism, neurogenesis, and so on (Kristian and Siesjo, 1998; Wang et al., 2007; Kinni et al., 2011). Relationships between exercise training and above-mentioned factors were summarized as follows.

Preclinical data suggested that the inflammation response played an important role in the brain damage following acute ischemic stroke (Wang et al., 2007). The neuronal damage aggravated leukocyte invasion, microvascular injury and the generation of free radicals (Wang et al., 2007). Many Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, were involved in the inflammation response after ischemic stroke (Berti et al., 2002). Exercise preconditioning could partially prevent hippocampal neuron apoptosis after cerebral ischemia in gerbils via regulating TNF-α and IL-1β levels (Park et al., 2013). The expression of intercellular adhesion molecule-1 (ICAM-1) was down-regulated by exercise preconditioning in ischemic rats during reperfusion (Ding et al., 2005).

In addition, pre-ischemic exercise could down-regulate the expression of Toll-like receptor-4 (TLR-4) and reduce cerebral injury (McFarlin et al., 2006) which could trigger a inflammatory cytokine cascade (Gleeson

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