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Research article

The ameliorative effects of exercise on cognitive impairment and white matter injury from blood-brain barrier disruption induced by chronic cerebral hypoperfusion in adolescent rats

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HIGHLIGHTS

- Treadmill exercise alleviated the cognitive impairment induced by CCH.
- Treadmill exercise prevents myelin degradation and damage to microvessels in the motor cortex and hippocampus after CCH.
- Treadmill exercise may provide protective effects on BBB disruption from overexpression of MMP-9 induced by CCH.
- Exercise may improve ischemic neurological disorders by reducing white matter injury and BBB disruption from overexpression of MMP-9 in the brain.

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ABSTRACT

Vascular dementia is the progressive change in blood vessels that leads to neuronal injuries in vulnerable areas induced by chronic cerebral hypoperfusion (CCH). CCH induces disruption of blood-brain barrier (BBB), and this BBB disruption can initiate the cognitive impairment and white matter injury. In the present study, we evaluated the effect of treadmill exercise on the cognitive impairment, white matter injury, and BBB disruption induced by CCH. Vascular dementia was induced by permanent bilateral common carotid arteries occlusion (BCCAO) in rats. The rats in the exercise group were made to run on a treadmill for 30 min once a day for 14 weeks, starting 4 weeks after birth. Our results revealed that treadmill exercise group was alleviated the cognitive impairment and myelin degradation induced by CCH. The disruption of BBB after CCH indicates degradation of occludin, zonula occluden-1 (ZO-1), and up-regulation of matrix metalloproteinases (MMPs). Treadmill exercise may provide protective effects on BBB disruption from degradation of occludin, ZO-1, and overexpression of MMP-9 after CCH. These findings suggest that treadmill exercise ameliorates cognitive impairment and white matter injury from BBB disruption induced by CCH in rats. The present study will be valuable for means of prophylactic and therapeutic intervention for patients with CCH.

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1. Introduction

Cerebral ischemia is one of the most common neurological disorders, and it is related to vascular dementia and Alzheimer's disease [1,2]. Vascular dementia is a progressive cognitive impairment that leads to neuronal injuries in vulnerable areas induced by chronic cerebral hypoperfusion (CCH) [3]. Permanent bilateral common carotid arteries occlusion (BCCAO) in rats has been used as the most popular animal model of chronic cerebral hypoperfusion ischemia [4,5]. Previous studies have shown that CCH induced by BCCAO in rodents has been proposed as an experimental model of neuronal degeneration and white matter damage, especially the hippocampus and corpus callosum [6,7]. It has been reported that BCCAO induced white matter injury in the hippocampus and corpus callosum, as well as learning and memory impairment [8–10]. There is wide agreement that learning and memory are dependent on the integrity of the white matter.

The neuropathological changes in these white matter lesions are associated with the blood-brain barrier (BBB) in vascular dementia [11]. The neurovascular unit of the BBB is composed

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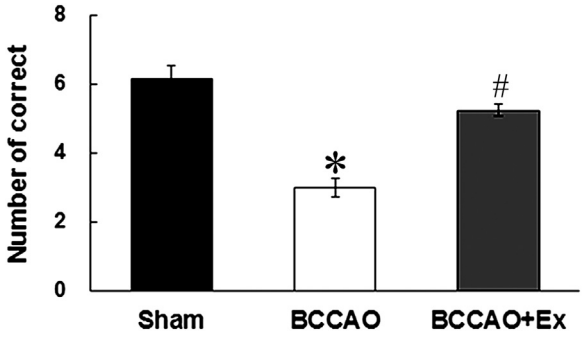

Fig. 1. Treadmill exercise alleviates memory impairment after CCH in the radial 8-arm maze task. The number of correct choices before the first error was counted in the radial 8-arm maze task. The data are presented as the mean ± S.E.M. $^{*}p < 0.05$, compared with the sham group. $\#p < 0.05$, compared with the BCCAO group.

of the microvessels, pods of astrocytes, neurons, and pericytes. The integrity of brain microvessels integrity requires maintenance of the endothelial permeability barrier. The cerebral endothelium forms the largest barrier in the brain, and the BBB is a highly selective permeability barrier, primarily formed by brain endothelial cells, which are connected by tight junctions such as occludin and zonula occluden-1 (ZO-1) [12]. When the BBB is damaged by various injuries, including ischemic stroke, BBB disruption generates the entrance of neurotoxic substances in the brain that lead to abnormal synaptic and neuronal functions [13]. Degradation of tight junction proteins of the BBB has been related to an increase in matrix metalloproteinases (MMPs) activity [14,15].

MMPs are calcium-dependent zinc-containing endopeptidase, and are capable of degrading all kinds of extracellular matrix proteins [16]. These have been considered as key molecules involved in the disruption of BBB after ischemia [17]. MMP-9 deficient knock-out mice are more protected against cerebral ischemia than wild-type mice [18]. Therefore, blocking MMP activation can be considered as a potential therapeutic intervention after CCH.

Regular physical activity is generally accepted as a means of promoting general health and well-being. Exercise is generally known to increase neuronal plasticity, alter the expression of various genes [19], and improve memory function [20] by inhibiting apoptotic neuronal cell death in the hippocampus [21]. Exercise may ameliorate neurological impairments in Alzheimer's and Parkinson's disease [22,23]. Many previous studies have shown that exercise reduces brain damage by decreasing cerebral permeability, MMP-9 expression, and brain integrity after ischemia [24,25].

Although the beneficial effects of exercise on chronic ischemia have been documented, it has not been well clarified whether treadmill exercise has some neuroprotective effect on BCCAO-induced cognitive impairment and white matter injury in rats. In the present study, we investigated the question of whether involuntary exercise ameliorates cognitive impairment and white matter injury from BBB disruption induced by CCH in rats.

2. Materials and methods

2.1. Experimental animals

Male Wistar rats (80 ± 10 g, 4 weeks old) were used in this experiment. The experimental procedures were performed in accordance with the animal care guidelines of the National Institutes of Health (NIH) and the Korean Academy of Medical Sciences. The rats were randomly divided into three groups (n = 10 in each group): The Sham group (Sham), the BCCAO group (BCCAO), and the BCCAO and treadmill exercise group (BCCAO + Ex).

2.2. Bilateral common carotid arteries occlusion (BCCAO)

Adult male Wistar rats (body weight 250–350 g, 12 weeks old) were anesthetized in 3% halothane in 70% N_2O and balance of O_2. The vessel occlusions were carefully performed to avoid damage of the surrounding tissue, particularly near the vagus nerve. For bilateral occlusion, a ventral midline incision was made to expose both carotid arteries. Each carotid artery was double-ligated with 3-0 silk (Ailee, Korea) just below the carotid bifurcation. Sham animals underwent the same operation procedure without vessel ligation.

2.3. Treadmill exercise protocol

The rats in the exercise group were made to run on a treadmill for 30 min once a day for 14 weeks starting 4 weeks after birth, according to the previously described method [26]. The treadmill exercise load consisted of running at 2 m/min for the first of 5 min, at 3 m/min for the next 5 min, and then at 5 m/min for the last 20 min at 0° of inclination. The rats in the non-exercise groups were left in treadmill without running for the same period as the exercise group.

2.4. Radial 8-arm maze task

Spatial learning was tested using a radial 8-arm maze apparatus, as previously described [27]. Four weeks after BCCAO, the number of correct choices on the radial 8-arm maze task was determined to evaluate special memory capability. A small receptacle filled with water (3 cm in diameter and 1 cm in depth) was located at the end of each arm. The rats were deprived of water for 48 h and then allowed to explore for water and to drink during a period of 8 min. Re-entry into the previously visited arms was counted as an error. In addition, the number of correct choices before the first error was counted.

2.5. Immunohistochemistry and immunofluorescence

Serial coronal sections of 40 μm thickness were obtained using a freezing microtome (Leica, Nussloch, Germany). For the visualization of myelin basic protein (MBP), rat endothelial cells antigen-1 (RECA-1) immunohistochemistry was performed. After being blocked with 10% normal hours and rabbit serum for 1 h, the sections were incubated overnight at 4 °C with MBP antibody (1:200; Abcam, Cambridge, UK), and RECA1 antibody (1:1000; Abcam, Cambridge, UK). The sections were then incubated for 2 h with the biotinylated rat and mouse secondary antibody (1:200; Vector Laboratories). The bound secondary antibody was then amplified using a Vector Elite ABC kit® (Vector Laboratories). The antibody–biotin–avidin-peroxidase complex was visualized using 0.02% DAB.

For immunofluorescence, the sections were incubated overnight at 4 °C with a mixture of two of the following primary antibodies: mouse monoclonal antibody to RECA1 (1:1000; Abcam, Cambridge, UK), and goat monoclonal antibody to occludin (1:500; LifeSpan BioSciences, Inc., Seattle, USA). The sections were then incubated with a mixture of Alexa Fluor 488-conjugated donkey anti-goat IgG and Alexa Fluor 594-conjugated goat anti-mouse IgG (1:1000; Molecular Probes, Eugene, OR) for 2 h at room temperature. Nuclei were visualized with 4′, 6-diamidino-2-phenylindole (DAPI).

2.6. Western blot analysis

Protein isolated from the motor cortex was prepared with a lysis buffer containing 50 mMTris-HCl (pH 7.5), 150 mM NaCl,

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