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Angiogenesis Induced by Physical Exercise in Adult Brain

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Although physical exercise has long been equated with better physical health, there are recently extensive researches showing that it has substantial benefits for the brain as well. Exercise does not only improve cognitive function in normal individuals, but it has also been associated with a lower risk for a variety of brain disorders. A model of the rehabilitative exercise in animal studies, enriched environment, which facilitates motor, sensory, and cognitive stimulations in housing conditions, increased neurogenesis and angiogenesis in the brain. Recent researches have attempted to identify molecular and cellular changes in the central nervous system elicited by physical activity. Animal studies have identified several key responses, especially neurorestoration via angiogenesis induced by physical exercise. This review focused on angiogenesis induced by physical activity such as enriched environment and physical exercise, and discussed its possible roles for functional recovery in the brain injury. **Vascular Neurology 2013;5:12-15**

Key Words Physical exercise, Enriched environment, Angiogenesis.

Introduction

In animal models, enriched environment consisting of running wheels, novel objects, and social interaction has been shown beneficial effects to enhance proliferation of neural stem/progenitor cells in the subventricular zone and to promote their migration to lesions, contributing to behavioral recovery.[1] Exposure to EE after brain injury has also been shown to provide neuroprotective effects, to reduce lesion size, to increase dendritic outgrowth, and to produce trophic factors.[2] EE changed astrocytic morphologies such as their size and density in the visual cortex,[3] and the outcomes of functional recovery by synergistically increasing angiogenesis coupled with astrocytic activation in the striatum.[4] Voluntary exercise was reported to increase the thickness of the motor cortex,[5] and the expression of trophic factors in the brain.[6-8] Exercise has been shown to induce angiogenesis in both cerebellum and motor cortex,[9,10] and to increase cholinergic and serotonergic neurotransmission.[11,12] Exercise has also been known to change the morphology of different blood vessels along the arterial tree,[13] to improve organ blood flow, and to cause functional changes.[14]

As a therapeutic mechanism, exercise induces vascular endothelial growth factor (VEGF) and neurotrophins.[15-17] Especially, both of EE and exercise increased fibroblast growth factor-2 (FGF-2), a strong pro-angiogenic factor,[18,19] acting as a mediator of the positive effects of exercise on the brain.[20] As does enriched environment, voluntary exercise also enhances neurogenesis in the hippocampus of adult animals.[21] Moreover, neurogenesis often appears in parallel with angiogenesis by exercise,[22] and angiogenesis can help satisfy the increased demand for oxygen and glucose by promoting delivery to active neurons.[23,24] Therefore, these studies suggest that angiogenesis acts a key role for neurorestoration in central nervous system (CNS) injury.

However, the therapeutic mechanisms how physical exercise affects the functional outcomes of the brain have been largely unknown. This review will provide an overview of angiogenesis, as a therapeutic mechanism, induced by physical activity in brain with normal condition and various neurological diseases with ischemic stroke and neurodegenerative diseases.

Physical Exercise in Intact Brain

The basic function of blood vessels is to supply oxygen and nutrients to the tissue. Any circumstance that compromises vascular function is bound to result in cellular dysfunction and eventually tissue atrophy or necrosis. Enriched environment increases the levels of angioneurins, molecules that affect both neural and vascular processes.[25] Angioneurins include molecules firstly described as vascular growth factors such as VEGF, and neurotrophins such as nerve growth factor, brain-derived

neurotrophic factor (BDNF), and neurotrophin-3.[15-17,26]

Apart from their effects on the production of new neurons in the dentate gyrus of the hippocampus, both enriched environment and exercise result in further morphological changes. Indeed, the functional changes associated with enriched environment might be due to not only enhanced neurogenesis but also the increases in gliogenesis, synaptogenesis and angiogenesis.[23,27]

Among the changes, it is well known that physical stimulation increases cerebral angiogenesis in healthy adult rodents.[9,23] Angiogenesis appears to be linked to neurogenesis in the SGZ of the hippocampal dentate gyrus, where clusters of proliferative neuronal progenitors are found in close proximity to capillaries and intermingled with dividing endothelial cells.[28] Physical exercise increases the proliferation of brain endothelial cells and angiogenesis throughout growth factors such as insulin-like growth factor (IGF) and VEGF that have an important role in both angiogenic and neurogenic effects of exercise on the brain.[29]

Physical Activity in Pathological Brain

Ischemic stroke

Stroke is one of the leading causes of long-term disability. It is associated with serious neurological impairment and persistent physical deficits. Among the interventions for stroke rehabilitation, physical exercise has been shown to be beneficial to brain function, and is widely used for functional recovery.

Neurovascular remodeling is a key component of recovery after stroke. Angiogenesis might play a critical part in the brain.[30] Current opinion supports the notion that angiogenesis promotes neurogenesis,[31] and that re-growth of vascular structures might provide the requisite molecular support for recovering neural networks.[32] It has been well documented that environmental stimulation in the form of physical activity counteracts the vascular dysfunction in neurological diseases such as stroke.[33,34] Treadmill exercise has been demonstrated that it could induce striatal angiogenesis and reduce neurologic deficits in ischemic rats.[35] Voluntary physical activity has been also reported to improve long-term stroke outcome related to improved striatal angiogenesis.[34]

Enriched environment enhances endogenous angiogenesis and neurobehavioral functions mediated by upregulation of FGF-2 in chronic hypoxic-ischemic brain injury.[19] Exercise also upregulates neurotrophic factors including BDNF and IGF-1, which may render brain tissue resistant to degenerative events.[36] Animals that exercise after brain injury show an increase in the expression of neurotrophic factors such as hepatocyte growth factor, BDNF, and FGF-2, which regulate neuronal survival and differentiation, synaptic plasticity as well as angiogenesis in the brain.[7,37]

The exercise-induced angiogenesis is specific to areas activated by the training.[38] Voluntary physical activity also improves long-term stroke outcome related with augmentation of angiogenesis and cerebral blood flow within the ischemic striatum.[34] In patients with ischemic stroke, the higher cerebral blood vessel counts correlated with longer survival.[39]

Neurodegenerative disease

Neurodegenerative changes in Alzheimer's disease (AD) and Parkinson's disease (PD) have been considered to result primarily from intrinsic neuronal defects. However, vascular abnormalities have been also identified in several neurodegenerative disorders. Since then, several reports have demonstrated vascular abnormalities in neurodegenerative diseases.[25]

Parkinson's disease is characterized by dopaminergic neuronal degeneration in the nigrostriatal system with clinical symptoms such as resting tremor, rigidity, bradykinesia, and postural instability.[40] Some reports have suggested that exercise increases anti-inflammatory proteins in patients with PD, thereby improving neuronal health.[41] VEGF has been reported to be upregulated in the substantia nigra, but not in the striatum of patients with PD.[42] VEGF administration showed positive effect on the angiogenesis and neurogenesis in the striatum of rat model of PD.[43] Transplantation of a VEGF-secreting cell line into the striatum of rats with PD demonstrated the potent neuroprotective effects on dopaminergic neurons.[43] Treadmill exercise also promoted angiogenesis through overexpression of VEGF in the brain of chronic PD mice.[22] Additionally, astrocytosis with angiogenesis induced by exercise might strengthen the neurovascular unit with subsequent microenvironmental amelioration in an animal model of PD.[44]

Alzheimer's disease is a neurodegenerative disorder that involves dementia mainly affecting the neocortex and hippocampus. The disease is characterized by two pathological hallmarks such as senile plaques and neurofibrillary tangles. Plaques are extracellular deposits of amyloid, consisting mainly of amyloid β (Aβ) peptide derived from proteolysis of the amyloid precursor protein by β- and γ-secretase.[45,46] A growing body of evidence suggests that neurovascular dysfunction in terms of aberrant angiogenesis and faulty clearance of Aβ peptide across the blood-brain barrier (BBB) contributes to neurodegenerative changes in AD.[47] Recent findings indicate that neurovascular dysfunction plays a pivotal role in cognitive decline and neurodegeneration in AD. Because of aberrant and insufficient angiogenesis,[48] faulty clearance of Aβ across the BBB associated with low levels of Aβ clearance receptor LRP1[49,50] or increased levels of its influx receptor RAGE[49,51] could lead to formation of vascular amyloid lesions and elevated fibrillar Aβ levels.[52,53] Increased vessel density by enriched environment provides the brain with a larger surface area for molecular transport exchange which is not only a supporting factor for a better supply with oxygen and nutrients in the brain, but also for better Aβ clearance across the BBB.[54]

Conclusion

Physical exercise induced angiogenesis within CNS under both intact and pathological conditions. Several pathologies that result in neural damage and degeneration may be shown in an early phase involving BBB disorder. Therefore, early treatment of the barrier could reduce the severity of neuropathological symptoms and facilitate recovery. Especially, endogenous angiogenesis induced by physical activity will contribute to amelioration of disease. In the future, detailed investigation of the mechanisms involved in both enriched environment and physical exercise could help in the design of therapies targeted at specific features necessary for neurorestoration.

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