



Research Review on Effects of Exercise on Neuroglial Cells after Central Nervous System Diseases

Mengqi Ma, Yu Wu

Zhejiang Normal University, Jinhua 321004, China.

Abstract: Astrocyte and microglia are two types of neuroglia that are relatively widely distributed and functionally important in the mammalian central nervous system. These two cells play an important role in CNS diseases. The mechanism of the effect of exercise on various CNS diseases is still unclear. In this paper, the effect of exercise on neuroglial cells after CNS diseases is investigated in depth from the function and structure of glial cells.

Keywords: Astrocyte; Microglia; Exercise; Alzheimer's Disease; Parkinson's Disease

1. Introduction

Neuroglial cells are widely distributed in the mammalian central nervous system and include astrocytes, microglia and oligodendrocytes^[1]. They have a wide range of roles, including supporting neurons that nourish the central nervous system, participating in the formation of the blood-brain barrier, and participating in the immune response. In central nervous system diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and traumatic brain injury, both astrocytes and microglia are closely related to the pathogenesis and development of these diseases^[2]. Currently, exercise has been shown to intervene in CNS diseases as a non-pharmacological intervention to affect astrocytes and microglia as well as brain trophic factors, but there is still a lack of in-depth understanding of the neuroprotective effects of exercise on CNS diseases. This article provides a review of the effects of exercise on glial cells after CNS disorders.

2. Astrocytes and microglia

Astrocytes are the most complex and abundant subtype of neuroglial cells in the central nervous system of all mammals, which originate from neuroepithelial-derived radial glial cells with protrusions extending from the cytosol and resembling a star, therefore it is named astrocyte^[3]. When CNS injury occurs, such as chronic hypoxia, astrocytes undergo reactive astrocyte proliferation, which involves multiple changes in cell proliferation, morphological changes, increased cell surface GFAP expression, gene sequence changes, and metabolic changes^[4], which astrocytes use to respond to acute injury. The increased immunopositivity of GFAP can be used as a ruler to judge the severity of injury^[5]. Activated astrocytes exist in multiple subtypes, and studies have shown that they are transformed more towards 2 subtypes, A1 RAS and A2 RAS, respectively, A1 is neurotoxic and is associated with various neurodegenerative diseases such as AD, while A2 is neuroprotective. A1 upregulates complement cascade genes, etc. and induces the production of pro-inflammatory factors with deleterious functions, and the A1 may have lost its pro-synaptic function, NF-kB can also awaken A1 and release complement C3^[6]. In contrast, A2 can upregulate many neurotrophic factors, thrombospondin and anti-inflammatory cytokines and protect neurons, but current studies have mostly focused on type A1 and further studies on the function of A2 are still needed.

Microglia are immunoreactive macrophages that reside in the CNS and are an important component of the NVU. It has the phagocytic ability to destroy invading pathogens, remove cellular debris and apoptotic cells left after cellular injury, and remove toxins and pathogenic foreign bodies from the nervous system to protect the CNS from infection, ischemia, injury, and disease, and always plays an important role in the immune response. Activated microglia are divided into two phenotypes according to their surface markers and functions, M1-type microglia and M2-type microglia, both of which highly express

IBA-1 on the cell membrane. IBA-1 is a marker protein on the surface of microglia, and the expression level of IBA-1 on the surface of microglia increases after activation [7]. After TBI, with the time of A small amount of pro-inflammatory substances can activate microglia M1, leading to the release of more pro-inflammatory cytokines, chemokines and ROS, which can damage normal cells and tissues and eventually lead to the formation of chronic inflammation.

3. Alzheimer's disease and parkinson's disease

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, characterized by memory and learning loss, behavioral impairment, and cognitive dysfunction, and its pathology is characterized by the accumulation of hyperphosphorylated tau protein and amyloid (A β) plaques, neuronal fiber tangle formation, neuronal loss, neuroinflammation, and oxidative stress etc . Conversely, astrocyte overexpression of NGF leads to neurotoxicity and degenerative loss of hippocampal neurons; after activation by A β or the appearance of injury, it is involved in the secretion of inflammatory cytokines IL-1, IL-6 and TNF- α , thus promoting the neurodegenerative process of AD^[8]. Microglia likewise play an important role in AD, and microglia dysfunction leads to the accumulation of A β plaques and tau proteins, which in turn can activate microglia and astrocytes via TLRs, releasing neuroinflammatory mediators and promoting neurodegeneration. However, in the later stages of AD, microglia transform to M1 type, which increases tau protein accumulation. Physical exercise has been shown to prevent AD, and an experimental animal study by Belaya et al. showed that voluntary physical exercise modulates the status of the RAS, which regulates the number of GFAP-positive astrocytes and the morphology of A β plaque-associated astrocytes in the hippocampus of 5xFAD mice, and that the molecular pathways involved in this regulation may be a therapeutic strategy for the treatment of AD^[9]. Zhang et al. showed that running exercise inhibited TREM2 shedding and maintained TREM2 protein levels while promoting brain glucose metabolism, microglia glucose metabolism and hippocampal morphological plasticity in AD mice. Regulation of microglia glucose metabolism and morphological plasticity by affecting TREM2 may be a new strategy for AD treatment^[10]. Parkinson's disease (PD) is a well-studied and common alpha-synaptic movement disorder, which is a progressive neurological degeneration caused by increased oxygen free radicals, mitochondrial dysfunction, protein degradation and aggregation dysfunction, and neuroinflammation resulting in a severe decrease in nigrostriatal tyrosine hydroxylase The pathology is characterized by the presence of a-synuclein deposits and protein inclusion bodies in the cytoplasm of neuronal cells^[11]. Astrocytes play an important role in the pathology of PD by promoting dopaminergic neurodegeneration. Upon uptake of α -synuclein, astrocytes are thought to release a variety of cytokines including TNF and IL-6, which induce an inflammatory response that promotes the progression of PD. Studies have shown that after running, GFAP expression decreases and the number of TUNEL-positive cells decreases, resulting in a decrease in the number of apoptotic cerebellar cells and protection of dopaminergic neurons, which leads to improved motor behavior^[12].

4. Conclusion

Both astrocytes and microglia have important roles in the mechanisms of action of various common CNS disorders, but the signaling pathways and mechanisms of action of various common CNS disorders are still unclear. There is no doubt that physical exercise can modulate microglia and astrocytes, affect neuroinflammation or neuronal cell survival, and thus provide targeted treatment for CNS diseases, but the intensity, type and duration of exercise and the mechanism of action need to be further investigated. It is expected to find a new direction for the future treatment of patients with clinical CNS diseases.

References

- [1] Subhramanyam, CS., Wang, C., Hu, Q., et al. Microglia-mediated neuroinflammation in neurodegenerative diseases[J]. *Semin Cell Dev Biol*, 2019, 94: 112-120.
- [2] Liu, M., Jiang, L., Wen, M., et al. Microglia depletion exacerbates acute seizures and hippocampal neuronal degeneration in mouse models of epilepsy[J]. *Am J Physiol Cell Physiol*, 2020, 319(3): C605-C610.
- [3] Kriegstein, A. and A. Alvarez-Buylla. The glial nature of embryonic and adult neural stem cells[J]. *Annu Rev Neurosci*, 2009, 32: 149-184.

- [4] Cunningham, C., A. Dunne, and A.B. Lopez-Rodriguez. Astrocytes: Heterogeneous and Dynamic Phenotypes in Neurodegeneration and Innate Immunity[J]. *Neuroscientist*, 2019, 25(5): 455-474.
- [5] Biesmans, S., P.D. Acton, C. Cotto, et al. Effect of stress and peripheral immune activation on astrocyte activation in transgenic bioluminescent Gfap-luc mice[J]. *Glia*, 2015, 63(7): 1126-1137.
- [6] Liddelow, S.A. and B.A. Barres. Reactive Astrocytes: Production, Function, and Therapeutic Potential[J]. *Immunity*, 2017, 46(6): 957-967.
- [7] Liu, LR., Liu, J.C., Bao, J.S., et al. Interaction of Microglia and Astrocytes in the Neurovascular Unit[J]. *Front Immunol*, 2020, 11: 1024.
- [8] Carter, SF., K. Herholz, P. Rosa-Neto, et al. Astrocyte Biomarkers in Alzheimer's Disease[J]. *Trends Mol Med*, 2019, 25(2): 77-95.
- [9] Belaya, I., M. Ivanova, A. Sorvari, et al. Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease[J]. *J Neuroinflammation*, 2020, 17(1): 271.
- [10] Zhang, SS., Zhu, L., Peng, Y., et al. Long-term running exercise improves cognitive function and promotes microglial glucose metabolism and morphological plasticity in the hippocampus of APP/PS1 mice[J]. *J Neuroinflammation*, 2022, 19(1): 34.
- [11] Real, CC., Suemoto, CK. Binda, KH., et al. Active lifestyle enhances protein expression profile in subjects with Lewy body pathology[J]. *Dement Neuropsychol*, 2021, 15(1): 41-50.
- [12] Real, CC., Garcia, PC., and Britto, L.R.G., Treadmill Exercise Prevents Increase of Neuroinflammation Markers Involved in the Dopaminergic Damage of the 6-OHDA Parkinson's Disease Model[J]. *J Mol Neurosci*, 2017, 63(1): 36-49.