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Mini Review

"NHE1: Protecting or Restoring the Blood Brain Barrier in Ischemic Stroke"

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Abstract

The Blood-Brain Barrier (BBB) plays an important physiological role in the Central Nervous System (CNS). In the case of ischemic stroke, damage to the BBB favors the development of a hemorrhagic stroke. Therefore, the study of treatments that allow the protection or, even better, the repair of the BBB may contribute to the reduction of the sequelae and the mortality rates in this disease. In this article, we focus on describing NHE1 and its association with the Wnt/β-catenin signaling pathway in IS.

Keywords: NHE1, Wnt, Beta-catenin, Ischemic stroke.

Abbreviations: BBB: Blood-Brain Barrier; IS: Ischemic Stroke; CNS; Central Nervous System.

Introduction

In recent years, analysis of pathophysiology and new strategies for treating IS have highlighted the importance of neurogenesis, the continuous generation of new brain neurons. It is important to study the regulation of neurogenesis because it has been shown that enhancing endogenous neurogenesis in ischemic injury and promoting the survival of new neurons improves the outcome of the disease [1,2]. Neurogenesis can be divided into several stages: activation of resting stem cells, proliferation, regulation of neuronal fate, maturation, and integration of new neurons [1,3], during which several molecular pathways are activated.

Ischemic Stroke (IS) presents as a focal, sudden, and non-convulsive neurological deficit; it is defined by the World Health Organization as a clinical syndrome consisting of rapidly progressive focal or global neurological signs, in the case of coma, lasting more than 24 hours or leading to death, without any apparent cause other than vascular origin [4]. In IS, the BBB undergoes altered Mechan transduction. As a result, ionic dysregulation and decreased nutrient transport have been identified, including the activation of several molecular pathways that modify tight junctions, modulate the expression of transporters, and can induce inflammatory damage in the BBB [5].

The BBB and the supporting cells that make up the neurovascular unit play a role in the protection and maintenance of homeostasis in the central nervous system. Astrocyte footprints cover 99% of the cerebrovascular surface and regulate BBB integrity and cerebral blood flow [5,6]. However, during IS, their function is altered and there is an overexpression of aquaporin 4, which promotes edema. In addition, the processes of vascular retraction trigger the opening of communicating junctions and the disassembly of endothelial tight junction proteins, leading to damage to the BBB [5,7]. In addition, astrocytes in IS persistently activate the protein NHE1, a Na+/H+ exchanger isoform 1. This leads to ionic dysregulation due to increased intracellular Na+. Therefore, neuroprotective effects against reactive astrogliosis in IS have been demonstrated by genetic ablation or pharmacological inhibition of NHE1, the major pH regulator in the CNS [8]. Inhibition or gene ablation of NHE1

showed decreased BBB permeability, increased angiogenesis, and increased blood flow perfusion; attributed to the preservation of BBB functions against astroglia injury in IS. However, in 2021 *Song S, et al.* [6] reported an association between NHE1 inhibition and activation of the Wnt/b-catenin pathway [6].

The Wnt/b-catenin signaling pathway is essential for the vascularization of the CNS and the formation of the BBB in the adult brain. Inhibition of this pathway in IS exacerbates BBB injury and promotes progression to hemorrhagic stroke. Pharmacologic activation of this pathway promotes maintenance of BBB integrity [9]. Activating the canonical Wnt pathway has been shown to modulate neurogenesis and neuroplasticity [1]. Inhibition or deletion of the NHE1 protein in astrocytes favors the activation of the Wnt pathway for the repair of the BBB after a stroke [6]. This new information encourages us to develop new therapies and to re-evaluate previous literature on neuroprotection.

Conclusion

Ischemic stroke is a multifactorial pathology that promotes injury through different molecular pathways, including inflammation, oxidative stress, astrogliosis, apoptosis, and hypoxia. The natural history of the disease implies that IS may progress to hemorrhagic stroke, so it is important to evaluate new treatments that can protect brain tissue in key structures such as the BBB, as well as research on the modulation of the Wnt pathway by the NHE1 protein to promote the process of neuronal repair and regeneration. The result will be a better understanding of brain function and the development of new treatment options.

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Conflicts of Interest

None.

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