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Review article

Astrocytes, therapeutic targets for neuroprotection and neurorestoration in ischemic stroke

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ABSTRACT

Astrocytes are the most abundant cell type within the central nervous system. They play essential roles in maintaining normal brain function, as they are a critical structural and functional part of the tripartite synapses and the neurovascular unit, and communicate with neurons, oligodendrocytes and endothelial cells. After an ischemic stroke, astrocytes perform multiple functions both detrimental and beneficial, for neuronal survival during the acute phase. Aspects of the astrocytic inflammatory response to stroke may aggravate the ischemic lesion, but astrocytes also provide benefit for neuroprotection, by limiting lesion extension via anti-excitotoxicity effects and releasing neurotrophins. Similarly, during the late recovery phase after stroke, the glial scar may obstruct axonal regeneration and subsequently reduce the functional outcome; however, astrocytes also contribute to angiogenesis, neurogenesis, synaptogenesis, and axonal remodeling, and thereby promote neurological recovery. Thus, the pivotal involvement of astrocytes in normal brain function and responses to an ischemic lesion designates them as excellent therapeutic targets to improve functional outcome following stroke. In this review, we will focus on functions of astrocytes and astrocyte-mediated events during stroke and recovery. We will provide an overview of approaches on how to reduce the detrimental effects and amplify the beneficial effects of astrocytes on neuroprotection and on neurorestoration post stroke, which may lead to novel and clinically relevant therapies for stroke.

Contents

Abbreviations: AQP, aquaporin; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CNTF, ciliary neurotrophic factor; CSPG, chondroitin sulfate proteoglycan; CST, corticospinal tract; DLX, distal-less homeobox; EPO, erythropoietin; GDNF, glia-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter; GLT, glutamate transporter-1; HMGB, high-mobility group box; IL, interleukin; iNOS, inducible nitric oxide synthase; KLK, Kallikrein-related peptidase; LTD, long-term depression; LTP, long-term potentiation; Mash, mammalian achaeteschute homolog; MCAo, middle cerebral artery occlusion; MMP, matrix metalloproteinases; MSC, marrow stromal or mesenchymal cells; mTOR, mammalian target of rapamycin; NGF, nerve growth factor; NMDAR, N-methyl-D-Aspartate receptor; NO, nitric oxide; OGD, oxygen-glucose deprivation; SDF, stromal cell-derived factor-1; SGZ, subgranular zone; Shh, sonic hedgehog; SOD, superoxide dismutase; SVZ, subventricular zone; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinases; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; TSP, thrombospondins EGF: vascular endothelial growth factor.

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1. Introduction

Stroke is the third leading cause of death in the United States and the leading cause of serious, long-term disability. Each year, Approximately 795,000 Americans suffer strokes, and more than 4000,000 people have survived a stroke and live with some form of neurological impairment or disability (Pearson-Fuhrhop and Cramer, 2010). One of the most common impairments after stroke is hemiplegia of the contralateral side to the affected cerebral hemisphere. Of stroke survivors, 50% have some hemiparesis, 30% are unable to walk without assistance, 26% are dependent in activities of daily living at 6 months after stroke, and approximately 15% to 30% are left permanently disabled (Duncan et al., 2005). Long-term disability from stroke not only affects functional status, but also has profound emotional and social effects on stroke survivors and their families, and has major economic consequences (Zorowitz et al., 2009).

Currently, intravenous administration of recombinant tissue plasminogen activator (tPA) is the only FDA approved therapy for acute ischemic stroke; however, due to the narrow therapeutic time window of 4.5 h after stroke onset and the risk of subsequent hemorrhage, only approximately 5% of patients benefit from this treatment (Fang et al., 2010). For decades, the primary approach and goal of therapy for stroke have focused on neuroprotection, to salvage ischemic neurons in the brain from irreversible injury, however, despite showing efficacy in experimental stroke models, all these efforts have failed to provide significant benefit in clinical trials of stroke (Han et al., 2013; Rother, 2008). The lack of translational success of neuroprotective agents is often attributed to differences between pre-clinical studies and clinical trials, such as population type (young animals in homogeneous population with no comorbidities, vs. elderly patients in heterogeneous population with numerous comorbidities); ischemic territory (restricted territory of MCA in animals vs. various vascular territories in humans); scope for optimization (optimized therapeutic time window, dose, and route of administration for animal studies, while not optimized for clinical studies); occlusion duration (controlled duration of occlusion in animal studies vs. variable occlusion duration in humans); primary endpoint (animal studies use infarct volume, while human studies use functional testing) (Minnerup et al., 2012; Stroke Therapy Academic Industry Roundtable, 2001). The consideration of using older animals and animals with comorbidities such as diabetes and hypertension, optimized dosage and time window of administration, as well as multiple physiological and neurological measurements, will hopefully improve the chances of successful translation for neuroprotection (Turner et al., 2013). More importantly, despite the fact that stroke affects all cellular elements of the brain, i.e., vascular cells, neurons, astrocytes, oligodendrocytes, microglia and ependymocytes, and induces signaling responses that occur within and between different cell types, most clinical trials were often performed using a single agent against single purported mechanism of action specifically targeting the neurons. Protecting neurons alone may be insufficient to improve neurological outcome after stroke. To accomplish this and to broaden treatment targets, we must consider therapeutic approaches that benefit multiple cell types, and in our view, particularly, astrocytes (Li et al., 2014). Astrocytes are likely to be essential targets for manipulation, because they are the most abundant subtypes of glial cells, by several fold outnumber neurons in the CNS, and are in contact with and interact and affect all parenchymal cells. Therefore, an increasing number of studies focus on the roles of astrocytes in stroke in recent years. Brain astrocytes are classically divided into several major types according to morphology and spatial organization: radial astrocytes surrounding ventricles, protoplasmic astrocytes in gray matter, and fibrous astrocytes located in white matter (Privat et al., 1995), as well as Bergmann glia in the cerebellum, velate astrocytes in the granule layer of the cerebellum, interlaminar astrocytes in the supragranular layers of the cerebral cortex, among others (Reichenbach and Wolburg, 2013). These cellular subtypes may differ not only phenotypically but also functionally, however, in this review, we will only use an umbrella term, astrocyte, neglecting the complexity, variety and distribution of assorted astrocytes.

2. Astrocytes in normal brain

As an integral part of the neuron–glia system, astrocytes provide many housekeeping functions, including structural support, formation of blood brain barrier (BBB), neuronal metabolism, maintenance of the extracellular environment, regulation of cerebral blood flow, stabilization of cell-cell communications, neurotransmitter synthesis, and defense against oxidative stress (Ransom and Ransom, 2012). Astrocytic finely