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Journal of the Neurological Sciences 267 (2008) 3 – 16

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Review

Dysfunctional astrocytes as key players in the pathogenesis of central nervous system disorders

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Received 9 June 2007; received in revised form 29 August 2007; accepted 30 August 2007
Available online 1 November 2007

Abstract

Once considered little more than the glue that holds neurons in place, astrocytes are now becoming appreciated for the key roles they play in central nervous system functions. They supply neurons and oligodendrocytes with substrates for energy metabolism, control extracellular water and electrolyte homeostasis, regulate neurotransmitter release, modulate immune responses, produce trophic factors, and control synapse formation. Astrocytes express receptors for many neurotransmitters, peptides, hormones and cytokines, and show excitability based on intracellular Ca^{2+} variations. Evidence is mounting that alterations in astrocyte functionality play a crucial role in the pathogenesis of disorders with diverse properties, including migraine, epilepsy, leukodystrophies, inflammatory demyelinating diseases, infections, brain edema and metabolic disorders, metal intoxications, neurodegenerative disorders, and schizophrenia. Targeting astrocyte dysfunction may lead to new therapeutic strategies for these disorders.

Keywords: Astrocytes; Glia; Astroglia; Diseases of the nervous system; Pathophysiology; Pathogenesis

Contents

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doi:10.1016/j.jns.2007.08.044

1. Introduction

Astrocytes are multifunctional cells that are indispensable for neuronal survival and function. They contribute to the formation and preservation of a secure blood-brain barrier (BBB), and their tight organization around the microvasculature provides anatomical evidence for the necessity of glucose to enter astrocytes on its way to neurons and other glial cells. Astrocytes are a reservoir of glycogen, which depending on the degree of neuronal activity is degraded to lactate that is delivered to neurons and oligodendrocytes as energy source (Fig. 1) [1–3]. Astrocytes control ionic and osmotic homeostasis, mediated by K^+ and water movements, predominantly through inwardly rectifying K^+ (Kir) channels (Kir4.1) and aquaporin-4 (AQP-4) water channels (Fig. 2) [4–7].

Astrocytes remove neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), norepinephrine, dopamine, serotonin, and acetylcholine from the synaptic cleft [4,8]. These neurotransmitters are then converted into metabolites that are utilized for alternative functions or secreted harmlessly into the extracellular space. Glutamate transporter-mediated uptake is critical for preventing the sustained activation of ionotropic glutamate receptors that would lead to excitotoxic cell death. Excitotoxicity involves sustained elevations of intracellular Ca^{2+}, which initiates a complex cascade of intracellular events that lead to destruction of the cell [9]. Glutamate released in the synaptic cleft is taken-up by astrocytes through Na^+-dependent excitatory amino acid transporters EAAT1 and EAAT2 (Fig. 3). In rodents, the homologs for the human EAAT1 and EAAT2 are called glutamate-aspartate transporter (GLAST) and glutamate transporter 1 (GLT1) [10]. Glutamate taken-up by astrocytes is amidated by the enzyme glutamine synthetase to form the non-neuroactive amino acid glutamine (Fig. 3). Glutamine is subsequently released by astrocytes for uptake by glutamatergic neurons, which deamidate it when they require glutamate for neurotransmission.

Astrocytes produce a variety of trophic factors including brain-derived neurotrophic factors, glial-derived neurotrophic factor, nerve growth factor, neurotrophins, and insulin-like growth factor I [11]. They have important roles in the development and plasticity of the central nervous system (CNS) by modifying the growth of axons and dendrites, and regulating synapse formation [12]. Astrocytes contribute to the control of immune responses in the CNS [13]. Signals that elevate intracellular levels of cyclic adenosine monophosphate (cAMP) inhibit astrocytic inflammatory responses [14], and the expression of adhesion, major histocompatibility complex (MHC) class II and costimulatory B-7 molecules [15,16]. Through the release of adenosine triphosphate (ATP), astrocytes are thought to mediate the extent of the neuroinflammatory response of microglia [17].

Astrocytes are coupled via gap junctions, which are mainly formed by connexins 30 and 43 [18]. Gap junctions consist of clusters of closely packed hemichannels, which align between neighboring cells head-to-head to form channels. They provide direct cytoplasmic passage of ions and small molecules such as glucose metabolites, second messengers and neurotransmitters. Ca^{2+}-mediated intercellular signaling is a mechanism by which astrocytes communicate with each other and modulate the activity of adjacent cells, including neurons, oligodendrocytes and microglia [19–21]. The propagation of intercellular Ca^{2+} waves might work by enhanced release of ATP, which activates purinergic receptors on neighboring astrocytes (Fig. 4) [22,23].

Astrocytes harbor receptors to a wide range of neurotransmitters, peptides, hormones and cytokines, which regulate their functional activities [4,24,25]. Neurotransmitters released in the synaptic cleft can also stimulate astrocytes