Ageing Research Reviews 18 (2014) 29–40

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

When astrocytes become harmful: Functional and inflammatory responses that contribute to Alzheimer's disease

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ARTICLE INFO

Article history:
Received 14 March 2014
Received in revised form 3 July 2014
Accepted 21 July 2014
Available online 28 July 2014

Keywords:
Astrocytes
Alzheimer's disease
Amyloid β metabolism
Cytokines
Neurodegeneration
Neuroinflammation

ABSTRACT

A growing body of research suggests that astrocytes play roles as contributors to the pathophysiology of Alzheimer's disease (AD). Several lines of evidence propose that activated astrocytes produce and release proinflammatory molecules that may be critical for the generation of amyloid-β peptide (Aβ). However, accumulating evidence indicates that Aβ may activate astrocytes, which leads to an increase in cytokines that has been suggested to be a causative factor in the cognitive dysfunction of AD; thus, a vicious circle may be created. Intrinsic inflammatory mechanisms may provide a regulatory system that is capable of influencing the neuronal microenvironment that affects neuronal survival. In this article, we address the evidence surrounding the interactions of dysfunctional astrocytes with neighboring neurons that may initiate a cascade of events that culminates with neuronal injury and the expression of the hallmark lesions of AD. Comprehensive knowledge of the molecular mechanisms underlying the participation of astrocytes in neurodegeneration could aid the development of therapies to restore proper astrocyte function that can be used in AD patients to prevent or alleviate the progression of the disease in a more efficient and comprehensive manner.

Contents

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http://dx.doi.org/10.1016/j.arr.2014.07.004
1568-1637/

1. Introduction

Dementia is a condition that results from a variety of brain diseases whose incidences have increased with the increase in life expectancy. The global incidence of dementia is estimated to be 35.6 million and is projected to nearly double every 20 years to reach 65.7 million in 2030. Alzheimer's disease (AD) constitutes 60 to 70% of dementia cases (WHO, 2012). Clinically, AD is defined by the progressive decline of memory, and histopathologically characterized by the presence of extracellular aggregates of amyloid-β (Aβ) peptide and intraneuronal neurofibrillary tangles that are composed of hyperphosphorylated tau protein. Aging is the main risk factor for late-onset AD, but it is possible that multiple neuronal abnormalities occur simultaneously in the brain and lead to the progressive disconnection of neuronal networks and the appearance of clinical symptoms. These alterations include genetic polymorphisms, epigenetic modifications, abnormal immune or inflammatory responses, traumatic brain injury, oxidative stress and mitochondrial dysfunction (Hardy, 1997; Podlesniy et al., 2013; Rao et al., 2012; Small, 1998). According to the amyloid cascade hypothesis, the deposition of Aβ in the brain initiates the pathological events that result in inflammation, synaptic dysfunction, synaptic loss and neuronal death (Walsh and Selkoe, 2004). Local and chronic neuroinflammation are constant features of AD brains, which are characterized by activated microglia and astrocytes that surround amyloid plaques and neurons that carry neurofibrillary tangles (Sastre et al., 2006).

2. Emerging roles of astrocytes in the brain

Astrocytes are the most abundant glial cells in the central nervous system (CNS) and play multiple roles in organizing and maintaining brain structure and function (Maragakis and Rothstein, 2006; Sofroniew and Vinters, 2010). Astrocytes dynamically modulate information processing and signal transmission, regulate neural and synaptic plasticity and provide trophic and metabolic support to neurons (Blackburn et al., 2009; Halassa and Haydon, 2010; Henneberger et al., 2010; Perea et al., 2009). Additionally, astrocytes regulate local CNS blood flow in response to changes in neuronal activity (Koehler et al., 2009). Indeed, a number of molecules, such as prostaglandins (PGE), nitric oxide (NO) and arachidonic acid (AA), that increase or decrease CNS blood vessel diameter and blood flow are produced by astrocytes (Gordon et al., 2007; Iadecola and Nedergaard, 2007).

Unlike neurons, astrocytes do not propagate action potentials along their processes; however, astrocytes do exhibit regulated increases in intracellular calcium concentrations $[Ca^{2+}]_i$ that represent a form of astrocytic excitability (Charles et al., 1991; Cornell-Bell et al., 1990; Nedergaard et al., 2003; Seifert et al., 2006). Increases in astrocytic $[Ca^{2+}]_i$ are of functional significance in astrocyte/astrocyte and astrocyte/neuron communication. Other physiological functions of astrocytes include the maintenance of fluid, ion, pH, and neurotransmitter homeostasis in the synaptic space (Sattler and Rothstein, 2006; Seifert et al., 2006; Simard and Nedergaard, 2004; Zador et al., 2009). After the reuptake of neurotransmitters into astrocytes, the neurotransmitters are metabolized and transformed into precursors that can be returned to the neurons to be converted into active neurotransmitters. In response to changes in neuronal synaptic activity, astrocytes are able to release gliotransmitters, such as purines and glutamate that affect neuronal excitability (Halassa et al., 2007; Nedergaard et al., 2003; Perea et al., 2009). Such evidence has given rise to the 'tripartite synapse' hypothesis, which states that astrocytes directly interact with neurons during synaptic activity in a manner that is essential for information processing in neural circuits (Araque et al., 1999; Halassa et al., 2007; Perea et al., 2009). This concept suggests that astrocytes, in coordination with pre- and post-synaptic neuronal elements, constitute a functional synapse (Agulhon et al., 2008). It was generally accepted that the astrocyte release of gliotransmitters is a $Ca^{2\pm}$-dependent process, but Fiacco et al. (2007) demonstrated that $Ca^{2\pm}$ elevations in hippocampal astrocytes do not affect the basal miniature excitatory activity. More recent evidence on the hippocampus has confirmed that the $Ca^{2\pm}$ increase in astrocytes does not affect the spontaneous or evoked excitatory action potential or short- and long-term plasticity at Schaffer collateral-CA1 synapses (Agulhon et al., 2010). Moreover, in 2012, the same research team found that $Ca^{2\pm}$ elevations alone are not sufficient for transmitter release by astrocytes, and additional factors, such as inflammatory molecules, appear to be required. Thus, astrocytes could be activated and transformed into competent gliotransmitter-releasing cells during the early stages of an inflammatory process that is associated with neurodegeneration (Agulhon et al., 2012).

Brain damage is accompanied by astrocytic activation (Fig. 1) that is characterized by the upregulation of glial fibrillary acidic protein (GFAP) and proliferative and morphological alterations (Kato et al., 1998; Pekny and Nilsson, 2005). Although activated astrocytes may provide neuroprotection via the release of neurotrophic factors, they also participate in inflammatory reactions by expressing pro-inflammatory molecules, such as cytokines and chemokines (Farina et al., 2007) that may participate in some neurodegenerative changes. Astrocytes throughout the entorhinal cortices of AD patients gradually accumulate Aβ42 species that positively correlated with the extent of local AD histopathology (Nagele et al., 2003). Although significant progress in the understanding of the function of astrocytes in the brain has been made over the last few decades, the cellular and functional responses of astrocytes to injury during the progression of AD are not completely understood (Attwell et al., 2010; Halassa and Haydon, 2010).

3. Astrocytic participation in cerebrovascular alterations in AD

Cerebrovascular dysregulation is an important feature of AD pathology that is associated with ischemic injury and brain-blood barrier (BBB) damage (Kalaria, 2000, 1999). Epidemiological studies suggest a relationship between AD pathology and cardiovascular disease and indicate that sporadic AD represents a cerebral vascular disorder that is caused by impaired neuronal perfusion (de la Torre, 2004) and/or by the accumulation of toxic products caused by altered BBB permeability (Zlokovic, 2014). Diverse studies in humans have demonstrated in vivo hypoperfusion in AD and that brain hypoperfusion–hypoxia, silent infarcts, stroke episodes and transient ischemic or hypoxic attacks increase the risk of AD (Vermeer et al., 2003). Photon emission computed tomography has been used to identify areas of initial hypoperfusion defects in parahippocampal gyri in patients with mild cognitive impairment that converted to AD (Park et al., 2011). Computer tomography studies have also revealed changes in the cerebral blood flow in the frontal cortex, temporal cortex, hippocampus, and basal ganglia in patients with AD (Tang et al., 2012). Of all of the cerebrovascular comorbidities found, cerebral amyloid angiopathy is the most common pathological finding. This condition is present in up to 90% of AD patients (Jellinger, 2002; Vinters, 1987) and may result from a failure to eliminate Aβ from the cerebral vasculature (Weller et al., 2009). Astrocytes are active participants of the neurovascular unit (NVU) formed by the collective action of neurons, astrocytes, pericytes and microglia. The NVU controls BBB permeability and cerebral blood flow, which are crucial in the maintenance of brain homeostasis. The astrocytic endfeet function as a barrier between