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Commentary

The role of astrocytes in amyloid β-protein toxicity and clearance

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ABSTRACT

The deposition of the amyloid β-protein (Aβ) in the brain is a pathological hallmark of Alzheimer's disease (AD). Here, Aβ deposits occur as Aβ plaques in the brain parenchyma and in the walls of cerebral and leptomenigeal blood vessels. Astrocytes are considered to be involved in the clearance of Aβ from the brain parenchyma into the perivascular space, across the blood–brain barrier, or by enzymatic degradation. As such it has been assumed that clearance of Aβ by astrocytes is beneficial. In a recent study published in *Experimental Neurology* Mulder et al. (2012; 233: 373–379) report changes in neprilysin and scavenger receptor class B member 1 gene expression in astrocytes exposed to fibrillar Aβ depending on the availability of amyloid-associated proteins, especially apolipoprotein E (apoE). Astrocytes from AD patients did not show this response in gene expression. Reactive astrocytes and Aβ containing astrocytes are common findings in the AD brain. A loss of excitatory amino acid transporter 2 expression in perivascular astrocytes of APOE ε4-positive AD cases and an alteration of neuronal apoE metabolism in the event of perivascular drainage of apoE–Aβ complexes has also been described. As such, reactive and compensatory changes in AD astrocytes compete with supporting functions of astrocytes finally leading to an impairment of metabolic support and transmitter recycling in the brain. In summary, exposure of astrocytes to increased amounts of Aβ over a long period in time very likely impairs the above mentioned supporting functions of astrocytes in AD patients because these cells have to clear large amounts of Aβ and, thereby, neglect their other functions.

Introduction

Alzheimer's disease (AD) is histopathologically characterized by the deposition of the amyloid β-protein (Aβ) in the brain (Glenner and Wong, 1984; Masters et al., 1985). Aβ plaques occur in the brain parenchyma (Masters et al., 1985). Aβ deposits in the vessel wall constitute cerebral amyloid angiopathy (CAA) (Glenner and Wong, 1984). Aβ deposition is the result of increased Aβ levels in the brain as demonstrated in amyloid precursor protein (APP) transgenic mouse models (Games et al., 1995; Sturchler-Pierrat et al., 1997). CAA in leptomeningeal and cerebral vessels can be seen in APP transgenic mice expressing APP and producing Aβ only in neurons indicating that neuron-derived Aβ is subject of clearance into the perivascular space where it aggregates at the basement membranes of cortical and leptomeningeal vessels (Calhoun et al., 1999).

The apolipoprotein E (APOE) ε4-allele is a major genetic risk factor for the development of AD (Strittmatter et al., 1993a). It is associated with increased Aβ deposition in the brain (Schmechel et al., 1993). Biochemically, the apoE E4 protein isoform tends to build complexes with Aβ more readily than the other apoE isoforms (Strittmatter et al., 1993b), thereby, presumably explaining the increased tendency to develop AD in ε4-allele carriers.

Astrocyte foot processes build the border between the extracellular space of the brain parenchyma and the perivascular space, i.e. the glia limitans, and control protein exchange between neurons and the brain extracellular space on the one hand and the perivascular space and the capillary endothelium on the other (Bechmann et al., 2007; Rolyan et al., 2011). In the AD brain Aβ-containing astrocytes have been described (Akiyama et al., 1996; Funato et al., 1998; Yamaguchi et al., 1998). It is hypothesized that astrocytes are involved in Aβ clearance in the AD brain and are, thereby, assumed to be beneficial (Thal et al., 2000; Wyss-Coray et al., 2003; Yamaguchi et al., 1998). In a recent study published in *Experimental Neurology* Mulder et al. (2012) demonstrate 1) that fibrillar Aβ together with apolipoprotein E (apoE) or serum amyloid P-complement C1q complexes (SAP-C1q) increases neprilysin (NEP) and scavenger receptor class B member 1 (SCARB1) expression in astrocytes and 2) that astrocytes from AD patients do not show this Aβ–apoE or Aβ–SAP–C1q complex induced increases in gene expression indicative for altered astrocyte function in AD. Here, I will discuss the current concepts about the role of astrocytes in AD in the light of these findings.

The role of astrocytes in the clearance of Aβ

Astrocytes of the glia limitans constitute the border between the brain parenchyma and the perivascular space of capillaries as well as of larger arteries and veins, i.e. the Virchow-Robin space (Bechmann

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et al., 2007; Thal, 2009). In so doing, glia limitans astrocytes take up proteins such as apoE–Aβ complexes from the extracellular space and degrade them (Wyss-Coray et al., 2003). Alternatively, astrocytes may secrete them into the perivascular space (Rolyan et al., 2011). From perivascular space apoE–Aβ complexes are either drained along the perivascular channels and along the basement membranes of the blood vessels into cervical lymph nodes and the cerebrospinal fluid (Carare et al., 2008; Weller et al., 2009) or cross the blood–brain barrier at the capillary level (Zlokovic, 2008). Astrocytes take up Aβ in complex with apoE through the $\alpha_2$macroglobulin receptor/low density lipoprotein receptor-related protein 1 (LRP1), in complex with apoJ (clusterin) through LRP2/Megalin receptors and in complex with SAP–C1q through yet unidentified acceptor sites (Deane et al., 2008; Koistinaho et al., 2004; Nielsen et al., 2010; Zlokovic et al., 1996). Astrocytes are capable of degrading Aβ enzymatically by NEP (Carpentier et al., 2002; Iwata et al., 2000), insulin-degrading enzyme (IDE) (Dorfman et al., 2010; Farris et al., 2003), or matrix metalloproteinase-9 (MMP-9) (Yin et al., 2006). Only in cases with AD-related pathology, i.e. in clinical and preclinical AD cases (Hyman et al., 2012) or in amyloid plaque-producing APP-transgenic mice significant amounts of Aβ are drained into the perivascular space but not in control cases or wildtype animals (Thal et al., 2007; Weller et al., 1998). In AD cases, Aβ-containing perivascular astrocytes were observed in the basal ganglia around enlarged perivascular spaces filled with an Aβ and apoE containing fluid (Utter et al., 2008). This accumulation of Aβ in astrocytes suggests a failure in the clearance of Aβ in AD. This leads to the conclusion that astrocytes play an important role for the clearance of Aβ.

AD-related alterations of astrocytes

In the AD brain different types of astroglial pathology can be distinguished (Table 1): reactive, hypertrophic astrocytes near amyloid plaques and neurofibrillary tangles (Dickson et al., 1988; Sheng et al., 1997), Aβ-containing astrocytes possibly involved in the removal of diffuse plaques and fleecy amyloid (Akiyama et al., 1996; Funato et al., 1998; Thal et al., 2000; Yamaguchi et al., 1998), and functionally impaired astrocytes with deficits in gene or protein expression (Mulder et al., 2012; Thal et al., 2010). Regardless the type of astrocytes, either from cortical, white matter, glia limitans, or subpial origin, the alterations in AD brain induce astroglial changes, that impair the physiological functioning of the astrocytes (Fig. 1, Table 1). In the event of a transformation into reactive astrocytes these cells react against Aβ or neurofibrillary tangle pathology rather than providing metabolic support of neurons, recycling transmitters, or clearing proteins including Aβ from extracellular space. As such, reactive changes in astrocytes presumably compete with their normal function. Likewise, an increased clearance of Aβ may also compete with the support of neurons, clearance of other proteins, and with transmitter recycling. Possible results of such a competition are the reduced NEP and SCARB1 gene expression in response to fibrillar Aβ–apoE treatment of astrocytes from AD patients compared with non-AD astrocytes in vitro (Mulder et al., 2012) and the reduced excitatory amino acid transporter 2 (EAAT-2) expression in perivascular astrocytes in AD cases carrying the APOE ε4 allele (Thal et al., 2010).

The role of apoE in astrocytes and its relation to AD

The physiological function of apoE is the transport of triglycerides and cholesterol from the liver into the peripheral organs and backward as a constituent of very low density lipoproteins (VLDLs) and high density lipoproteins (HDLs) (Mahley, 1988). In the brain parenchyma apoE is mainly produced by astrocytes but also taken up and metabolized by astrocytes (Pitas et al., 1987). Neurons contain only small amounts of apoE (Han et al., 1994) that is under physiological conditions metabolized by the neurons but not subject of astroglial clearance (Huang et al., 2001; Rolyan et al., 2011). Astrocytes are important for the lipid metabolism of the brain. Secretion of apoE containing lipoproteins into the perivascular space by astrocytes is one physiological mechanism in this regulation of lipid metabolism and transport (Rolyan et al., 2011; Thal et al., 2007). Astrocytes express LRP1 (Moestrup et al., 1992). LRP1 is a receptor for the uptake of apoE, apoE-containing lipoproteins (Herz et al., 1988), and also of apoE–Aβ complexes (Koistinaho et al., 2004). Blocking this receptor with its receptor associated protein (RAP) or blocking the apoE–Aβ interaction by anti-apoE antibodies inhibits uptake of apoE–Aβ complexes by astrocytes (Koistinaho et al., 2004; Rolyan et al., 2011; Wilhelmus et al., 2007) indicating that LRP1 and apoE are of major importance for Aβ clearance by astrocytes in vivo. Mulder et al. (2012) showed in vitro that fibrillar Aβ–apoE preparations increased expression of NEP and SCARB1 gene expression presumably aimed at stimulating further uptake of Aβ via SCARB1 and its degradation by NEP in the normal astrocytes. Such an increase of NEP and SCARB1 gene expression was not seen in astrocytes taken from AD patients (Mulder et al., 2012) indicating that these cells are already altered in AD. The detection of Aβ-containing perivascular astrocytes in AD cases (Utter et al., 2008) further supports the hypothesis that astroglial apoE-related clearance of Aβ is impaired not only by insufficient intracellular degradation but also by an impaired secretion into the perivascular space. Another argument for an apoE-related alteration of astrocytes in AD cases is our recent finding that APOE ε4 allele carriers with AD exhibit a distinct histopathological pattern including capillary CAA and a reduced astroglial EAAT-2 expression in perivascular astrocytes that distinguished these individuals from non-ε4 AD cases (Thal et al., 2010). In addition to astrocytes, pericytes

Table 1
Types of astrocytes in normal and AD brain.

Type of astrocytes	Marker protein	Anatomical localization	Potential function
Physiologically occurring astrocytes			
Cortical, protoplasmic astrocyte	EAAT-1, EAAT-2, (GFAP)	Cortex neuropil	Glutamate recycling, metabolic support
White matter, fibrous astrocytes	GFAP	White matter	Metabolic support, protein clearance
Glia limitans (perivascular) astrocytes	GFAP	Glia limitans (perivascular gray and white matter)	BBB: metabolic support, protein clearance
Subpial astrocytes	GFAP	Subpial gray matter	CSF–brain barrier: metabolic support, protein clearance
AD-related pathological types of astrocytes			
Reactive, hypertrophic astrocytes	GFAP	Near amyloid plaques, near neurofibrillary tangles	Reactive response to pathological proteins/cells
Aβ containing astrocytes	GFAP, Aβ	Near diffuse plaques and fleecy amyloid, perivascular and subpial gray and white matter	Aβ clearance — state of decompensation
Functionally impaired astrocytes	GFAP and loss of EAAT-2 expression	Perivascular cortex	Loss of physiological properties

EAAT = excitatory amino acid transporter, GFAP = glial fibrillary acidic protein, BBB = blood–brain barrier, CSF = cerebrospinal fluid, Aβ = amyloid β-protein.