Astrocytes Involvement in AD

Subjects: Others

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Astrocytes, the most numerous glia cells in the brain, have many housekeeping functions, maintain the homeostasis of the CNS and are responsible for neuroprotection and defense. Long regarded as a non-specific, mere consequence of AD pathology, activation of astrocytes is now considered a key factor in both initiation and progression of the disease, and suppression of astrogliosis exacerbates neuropathology. Reactive astrocytes overexpress many cytokines, chemokines, and signaling molecules that activate or damage neighboring cells and their interplay with microglia and neurons can result in virtuous/vicious cycles which differ in different brain regions. Heterogeneity of glia, either between or within a particular brain region, is likely relevant in healthy conditions and disease processes. Understanding the spatial differences and roles of glia will allow assessing how those interactions can influence the state and progression of the disease, and will be critical to identify therapeutic strategies.

Keywords: A1 astrocytes ; A2 astrocytes ; Alzheimer’s disease ; hippocampus ; clasmatodendrosis ; neuroinflammation ; neurovascular unit ; glymphatic system ; beta amyloid ; glia

1. Introduction

In the healthy brain, astrocytes regulate the formation, maturation, and plasticity of synapses [1][2], are indispensable for neurotransmitter homeostasis [3][4], and control the formation of neural circuits [5][6][7][8][9]. Astrocytes release gliotransmitters [10][11][12][13] necessary for synaptic plasticity [12][14], and control GABA and glutamate extracellular levels at the synapses. Astrocytes mediate the synaptic functions [15][16] and are thus involved in memory formation [12][13][14][17][18]. Healthy astrocytes are fundamental cells of the neurovascular unit, and help maintaining the integrity and the functionality of the BBB and of the glymphatic system [19][15][20][21][22]. It has been proposed that vascular dysregulation and breakdown of the BBB may be one of the first steps in AD pathogenesis [23][24], affecting Aβ clearance [25]. Furthermore, the glymphatic system facilitates the clearance of interstitial solutes including Aβ and tau [26]. Astrogliosis causes loss of AQP4 polarization in perivascular astrocytes, which may represent a mechanism common to neurovascular unit (NVU) and glymphatic dysfunctions in many neurodegenerative diseases such as AD [27][28]. It has been shown that the glymphatic function is disrupted around microinfarcts, especially in the aging brain [26]. All these data taken together may suggest that microlesions of the neurovascular unit, also disrupting the glymphatic system, may trap proteins within the brain parenchyma, increasing the risk of amyloid plaque formation [26].

2. Astrocytes in pathological mechanisms

Yet, the understanding of the multiple, contrasting roles of astrocytes in pathological mechanisms entered into focus only very recently. Pathological phenotypes of astrocytes are responsible for three major responses to insults: (i) reactive astrogliosis, (ii) astroglial atrophy and loss of function and (iii) pathological remodeling [29][30].

In AD patients and in amyloid-mouse models of AD [31][32][33][34], astrocytes have high levels of GABA. In two different mouse models of AD, APP/PS1 mice (APP KM670/671NL (Swedish), PSEN1 L166P) [32] and 5xFAD mice (APPSwFlLon, PSEN1*M146L*L286V) mice [34], tonic release of GABA from hypertrophic astrocytes [32][33][34] located in the vicinity of Aβ plaques was demonstrated. At first, release of GABA from astrocytes, activating GABAA and GABAB receptors, causes a decrease in glutamate release, with a consequent decrease in excitotoxicity and neuroinflammation [35]. Later, the excess of GABA can unbalance the subtle inhibitory–excitatory equilibrium in the neuronal network, inducing inhibition of synaptic plasticity [33]. It has also been shown that astrocytes degeneration may cause the downregulation of glutamate transporters. The two most expressed isoforms of glutamate transporters in the hippocampus are EAAT-1 (Excitatory amino acid transporter-1, GLAST in rodents), and EAAT-2 (Excitatory amino acid transporter-2, GLT1) [36], mainly expressed on astrocytes. Decreased expression of either one or both glutamate transporters compromises the ability of astrocytes to reuptake the excess of glutamate, and to regulate glutamatergic transmission. This in turn results in severe

excitotoxicity that underlies rapid development of severe dementia, as shown in Wernicke encephalopathy [37][38]. In AD pathogenesis the situation seems still controversial. In AD patients, the Aβ peptide has been shown to downregulate the functional activity of glutamate transporters [39]. However, in a subsequent study, the Aβ peptide was reported to increase the cell surface expression of GLAST and augment the glutamate clearance ability of cultured astrocytes [40]. Nevertheless, it has been reported that impairment of glutamate uptake is involved in the pathogenesis of AD and other neurodegenerative disorders such as Parkinson's disease, Huntington's disease, and epilepsy (reviewed in detail elsewhere [41][42]).

3. Astrocytes in AD

In AD, in different brain regions and subregions, astrocytic modifications are highly heterogeneous and can result in either hypertrophy or atrophy [43][44][45][46]. In a triple transgenic mouse model of AD, Aβ plaques trigger astrogliosis, which is, however, different among brain regions. Indeed, Aβ causes hypertrophy of astrocytes mainly in the CA1 region of the hippocampus [43][47] while in the entorhinal and prefrontal cortex it causes little sign of astrogliosis [48][49]. Furthermore, in the hippocampus hypertrophic astrocytes are located in close proximity to Aβ plaques, both in animal models [47] and in post mortem brain tissue from AD patients [50][51], a strategic location that is considered neuroprotective. Indeed, it has been demonstrated with PET (Positron Emission Tomography) scan in human patients that the decrease in astroglial reactivity parallels the switch from mild cognitive impairment to AD, again demonstrating the neuroprotective role of astrogliosis, at least in the prodromal phases of AD [46]. More distantly from the plaques, astrocytes look atrophic [47].

Recent studies have demonstrated that different CNS injuries stimulate at least two types of astrocytes with strikingly different properties, A1 reactive astrocytes, with detrimental properties for neurons, and A2 reactive astrocytes with beneficial, neuroprotective properties. Indeed, A2 reactive astrocytes release neurotrophic factors and cytokines that promote neuronal survival and neurogenesis, as well as synaptogenesis and repair of the damaged synapses. Among the neurotrophic factors or cytokines released by A2 astrocytes are BDNF, IL-6, CLCF1, GDF15, and thrombospondins. In addition, A2 astrocytes release gliotransmitters such as glutamate, GABA, ATP, and neuromodulators such as kynurenic acid and d-serine [52][53]. In the presence of high levels of proinflammatory cytokines, activated astrocytes increase ROS and NO production through induction of the NF-κB pathway [54]. A1 neuroinflammatory astrocytes upregulate many genes that express proinflammatory proteins and other neurodegenerative substances [52]. Recently it has been demonstrated that astrocytes in their A1 state release factors that are toxic to neurons and oligodendrocytes, and lose their phagocytic activity and possibly their ability to dispose of Aβ plaques [53]. Suppression of astroglial reactivity and phagocytosis exacerbates Aβ load and reduces neuroprotection [55].

Although astrocytes so far have been shown to acquire these two distinct reactive states, more recently it has been postulated that they may acquire many possible activated states in both the healthy and diseased brain (also see [56]). These different states depend not only on the type of insult but also on the brain structure in which they are located [52]. Indeed, nine different groups of astrocytes have been defined [57]. This result possibly indicates that astrocytes acquire a reactive phenotype in function of the local microenvironment, even in healthy conditions [57].

Nevertheless, it is not understood completely yet whether astrocytes located in different cerebral structures respond to the same insult with the same morphofunctional modifications or whether they react differently to the same insult. In other words, whether astrocyte responses to injuries are controlled by intrinsic cues, or whether they depend upon external signals that come from the environment [58][59]. A third hypothesis is that there may exist a continuum in the diversity and intensity of astrocyte reaction, which possibly hides different, discrete reactive states. Recent work has demonstrated that astrocytes located in distinct anatomical regions have different molecular profiles [60][61], suggesting that astrocytes have site-specific functional roles. Astrocytes derived from different CNS regions respond differently to Aβ in vitro [62]. Indeed, this finding indicates that astrocyte heterogeneity is at least partially intrinsic, possibly due to preexisting differences between astrocytes from distinct brain regions [63][60][64][65][66][67][68]. In the mouse, hippocampus specific, age-exacerbated reactive astrogliosis causes higher vulnerability to age-related neurodegeneration [69]. For instance, an age-related morphofunctional modification of astrocytes called clasmatodendrosis, has been found in the rat hippocampus [70][71][72][73][74]. Indeed, in the white matter of patients with cerebrovascular dementia and AD [75], and in patients with mixed dementia [76], astrocytes show clasmatodendrosis, which correlates directly to changes in cell function [77]. Clasmatodendrotic astrocytes have swollen and vacuolized cell bodies, shorter branches, and loss of distal processes that cause less endfeet coverage of brain vessels. These latter modifications can contribute to vascular deficits observed during aging and in AD. Furthermore, since astrocyte endfeet are main components of the BBB, their fragmentation by clasmatodendrosis can contribute to the impairment of the functionality of the barrier. Aβ clearance is essential for neuroprotection against AD, and in mouse models of AD the impairment of Aβ clearance increases neurodegeneration [78]. The deposition of high quantities of fibrillar Aβ modifies the interactions between astrocytes and neurons [71], possibly

decreasing Aβ peptide disposal to the circulating system, and consequently, increasing Aβ deposition in brain parenchyma [79] that may play a significant role in neuronal damage. Therefore, clasmatodendrosis can hamper astrocyte-mediated Aβ clearance from neurons and increase fibrillar Aβ deposition [71][80].

It has been shown that Aβ reacts with receptors located on astrocytes such as CD36 (cluster of differentiation 36), RAGE (receptor for advanced glycation end products), SCARA-1 (scavenger receptor A-1), and MARCO (macrophage scavenger receptor with collagenous structure). RAGE is one of the most characterized scavenger receptors, and binding to Aβ causes proinflammatory modifications in astrocytes [81]. RAGE mediates the phagocytic profile of astrocytes [82] and the interaction with other ligands, including S100β, involved in AD neuroinflammation [83]. SCARA-1 is involved in Aβ clearance [61], while MARCO may decrease the inflammatory response of microglia [84], and CD36 and RAGE are implicated in the scavenging activity of microglia caused by Aβ (for references see [85]). CD36 cooperates with toll like receptors (TLR-6 and TLR-4), causing ROS production and inflammasome activation [86]. We know that expression of many proinflammatory proteins is increased in astrocytes but, interestingly, not only genes that are upregulated but also those that are down regulated may help understand the roles of reactive astrocytes in disease pathogenesis. However, no established list of down-regulated genes across multiple diseases and especially in AD so far exists [87]. To make things even more complicated, in an animal model of AD different proinflammatory proteins are expressed at different levels in astrocytes located in different areas within the hippocampus [43]. Indeed, molecular changes in astrocytes are highly context-specific, with about 50% of modified gene expression that depends on the type of brain damage [88].

It has been shown that astrocytes can participate with microglia in phagocytic events [89][90][91][92][93]. Astrocytes use the ABCA1 [92], MEGF10, and MERTK [94], as well as BAI1 and integrin αvβ3 or αvβ5 [95] pathways for phagocytosis. Since astrocytes are not as mobile as microglia [96][97], they are not able to migrate, but polarize their distal processes, and engulf apoptotic bodies derived from dendrites of dying neurons or other toxic material such as Aβ. Astrocytes and microglia play orchestrated roles in a highly coordinated way, with differences in different brain areas that can have important physiopathological consequences [92]. Reactive astrocytes have dual roles in Aβ plaque degradation. The phagocytic role of reactive astrocytes in amyloid pathology may contribute to the clearance of dysfunctional synapses or synaptic debris, thereby restoring impaired neural circuits and reducing the inflammatory impact of damaged neurons [98].

Notwithstanding all this new evidence, the role of astrocytes in AD is still controversial. On one side, astrocytes are able to remove Aβ fibrils from neuron membranes [80] for their disposal [79]. On the contrary, it has been demonstrated that astrocytes may also contribute directly to Aβ peptide overproduction especially in the presence of increased cellular stress caused by environmental factors and increased neuroinflammation [80][99][100][101][102][103]. On the other side, a decrease in the size of astrocytes and reduction in the number of GFAP-positive primary branches is observed in the hippocampus, prefrontal cortex, and entorhinal cortex at the early stages of the pathology in mouse models of AD [47][48][104][105]. These phenotypic modifications can possibly cause decreased Aβ disposal and increased Aβ extracellular levels.

In the healthy brain, astrocytes are organized in non-overlapping domains while reactive astrocytes lose their domain organization. The significance of astrocytic domains in health and their spatial dysregulation in disease remains unclear. Many chronic neurological disorders are accompanied by chronically stressed, degenerated, and atrophic astrocytes with loss of function, which adds to the progression of the disease. At the early stages of AD, gliosis is markedly increased, and reactive astrocytes are located around Aβ plaques [47][106][107], while large numbers of astrocytes undergo atrophy [108]. In these conditions, astrocytes undertake a series of phenotypic and functional changes [109] that lead to the formation of a sort of scar around the plaque. Scar formation starts as a defensive reaction aimed at the isolation of the plaque from the healthy tissue for neuron survival. To this aim, astrocytes release neuroprotective agents such as BDNF, VEGF, CLCF1, thrombospondins and bFGF, or IL6 and GDF15 [109].

4. Conclusions

Whether glial cells adopt phenotypes that aggravate tissue injury or promote brain repair, most likely depends on different sets of factors, such as the nature of the damaging element, the time course of injury, the severity score that determine the precise arrangements of signals deriving from the surrounding environment. Therefore, the response is possibly not univocal but largely depends on the disease context.

The idea that the same stimulus/injury activates different types of astrocytes cells in different regions of the brain raises many questions. How many reactive astrocytescell types are there? What are the cell-cell interactions that induce reactive astrocytes? What are the relevant extracellular and intracellular signaling pathways that induce reactive astrocytes?

Answering to all these questions will shed light on how those interactions can influence the disease state, the progression of the disease, and will be critical to identify therapeutic strategies for recovery.

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