

The Role of Astrocytes in Astrocytes Alzheimer's Disease

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Abstract

Astrocytes are highly specialized glial cells and play a crucial role in neuronal functionality and brain functional integrity. Although research on Alzheimer's disease has been concentrated mainly on the role of neurons, increasing evidence comes to light marking the important role of astrocytes in the pathophysiology of Alzheimer's disease. Astrocytes undergo certain morphological changes in Alzheimer's disease and they are thought to participate in Ab metabolism, and to mediate neurotoxicity and neuronal death through Calcium signaling. Here we briefly present the morphological changes of astrocytes and their role in Alzheimer's disease neurodegeneration.

Keywords: Astrocytes, Alzheimer's disease, Ab clearance, calcium signaling.

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Introduction

Astrocytes are highly specialized and of heterogeneous morphological appearance glial cells that play a crucial role in the neuronal functionality and overall integrity of brain function. They can be distinguished based on their morphology and biochemical characteristics to protoplasmic ones which are located in the cerebral and spinal gray matter, and usually have 5-10 primary processes with extremely elaborate branches, to fibrous astrocytes, which are located in the white matter, and have long processes that parallel to neuronal axons, to radial glia, which are commonly seen in the developing brain and have an ovoid body with to antidiometric elongated processes, and after brain maturation are found only in the retina and the cerebellum, to velate astrocytes which are protoplasmatic astrocytes, located in the cerebellar molecular layer, to astrocytic neural stem cells which are found in the subventricular zone of the lateral ventricle and to pituicytes of the neurohypophysis [1].

For more than 100 years neurological research has focused mainly on neurons, ignoring other types of cells of the central nervous system, however recent studies have shown that glial cells and more specifically astrocytes are of extremely high importance for the normal function of neurons and the central nervous system, and might have significant roles in the pathogenesis of many neurological diseases and conditions, while they offer structural support, participate in the modulation of the neuronal activity and neuronal metabolism, they play a role in the maintenance of the extracellular environment and the regulation of cerebral blood flow, they are an integral part of the defense against oxidative stress and can act as pluripotent neural precursors for adult neurogenesis [2, 3].

Increasing evidence is stressing the emerging role of astrocyte dysfunction in the pathophysiology of neurological disorders, including epilepsy, migraine and Alzheimer's disease [4, 5].

In the present study, we aim to review the role of astrocytes in the metabolism and clearance of Ab peptide and their role in Ab-induced neurotoxicity in Alzheimer's disease.

Connectivity and synaptic activity - Role of astrocytes in synaptic regulation

Astrocytes can exhibit evoked inward currents, and although they do not propagate action potentials along their processes, they seem to play an important role in the modulation of neuronal synaptic activity [4]. Astrocytes can couple to neighboring cells (other astrocytes, oligodendrocytes and rarely neurons) through gap junctions, formed by connexins, providing a powerful communication network, permeable to both small ions and some larger macromolecules. Furthermore, they express potassium and sodium channels and exhibit regulated increases in intracellular calcium concentration [4,6]. The increase of the intracellular calcium concentration can occur as intrinsic oscillation resulting from calcium released from intracellular stores, can be triggered by transmitter such as glutamate and purines, can elicit the release of transmitter into extracellular space including glutamate, ATP, and D-serine, that bind to pre- and/or postsynaptic neuronal receptors to modulate synaptic transmission and activity, and can be propagated to neighboring astrocytes [7 - 10].

The integrity in the cooperation between neurons and glial cells is of crucial importance for the maintenance of cognitive functions (11, 12). Astrocytes in particular release gliotransmitters which control synaptic plasticity in different brain structures (13, 14, 15), and are involved in memory and learning processes. The dysregulation of this relationship may result in different neurodegenerative disorders and psychiatric conditions (16 - 19).

Reactive astrogliosis in AD

Astrogliosis is common in all kinds of CNS injury, however, increased astrocyte reactivity is a telltale sign of chronic neurodegenerative diseases like Ad and PD [20 - 22]. Recent evidence identifies two different types of astrocytes with specific roles in neurodegeneration, A1 and A2 astrocytes. Although type A2 astrocytes play a more general role in advance healing of ischemic injuries, reactive A1 astrocytes may be involved in detrimental activities [23].

Reactive astrogliosis is one of the archetypical morphological features in Alzheimer's disease brains, manifested by cellular hypertrophy and an increase in the expression of GFAP and astroglial S100B protein [24 – 30]. Post-mortem analysis of Alzheimer's disease brains has also demonstrated a positive correlation between the degree of astrogliosis and cognitive decline, but not with senile plaque pathology [31]. The same study describes a link between reactive astrocytes and a number, but not all the Amyloid plaques, whilst astrogliosis was present even without Amyloid depositions in both AD and non-AD brains. The question that arises then is whether astrogliosis can just accompany normal brain aging, however, experimental evidence in rat retina showed that aging was associated with a decrease in the total number of astrocytes, with an increase in the proportion of cells with gliotic morphology [32, 33]. Conversely, other studies have reported a significant increase in the number of astrocytes in the hippocampus of aging mice and in the frontal cortex of male rats, accompanied by hypertrophic remodeling in the cortex [34]. Further studies revealed an increase in the number of astrocytes in the parietal cortex and the dentate gyrus of old Wistar rats [35, 36], and no significant changes in the astrocytic number were found in the primary visual cortex of old rhesus monkeys [37]. Another study found a significant increase in GFAP expression and astroglial hypertrophy in the white matter of the brains of aged monkeys [38], and studies in the human neocortex did not reveal significant changes in the number of astrocytes with age [39]. Although the link between normal aging and astrogliosis remains controversial, it widely accepted at the moment that an increase in the number and an overall astrocytic hypertrophy are features of normal brain aging [40].

Morphological changes of astrocytes driven by Ab

Exposure to Ab triggers certain morphological changes of astrocytes in primary mixed neuronal-astrocytic cultures characterized by convoluted processes and terminal swelling [41]. The activation of astrocytes in response to Ab is closely associated with Ab-induced neuronal death, and as Garwood et al have shown, Ab-induced neuronal death is mediated by a soluble factor secreted by astrocytes [41]. Furthermore, astrocytes increase Ab-induced caspase-3 activity in primary mixed cultures, which in turn is closely linked to neuronal

death. Another important even in AD pathophysiology is the phosphorylation of tau protein, induced by Ab peptide [42]. Experimental evidence has shown that astrocytes are necessary for Ab-induced phosphorylation [41]. Ab treatment of mixed neuronal-astrocytic cultures had a significant effect on the release of inflammatory cytokines including cytokine-induced neutrophil chemoattractant, interferon gamma, interleukin 1b, 1ra, 6, 13, 17, IP-10. Some of these inflammatory mediators are related to neurotoxicity and are known to trigger caspase activation through death effector domains [42].

The activated astrocytes are intimately involved in the neuroinflammatory component of the AD through the release of cytokines, pro-inflammatory factors, and nitric oxide/reactive oxygen species neurotoxicity [43].

These aspects can also be seen in Figure 1.

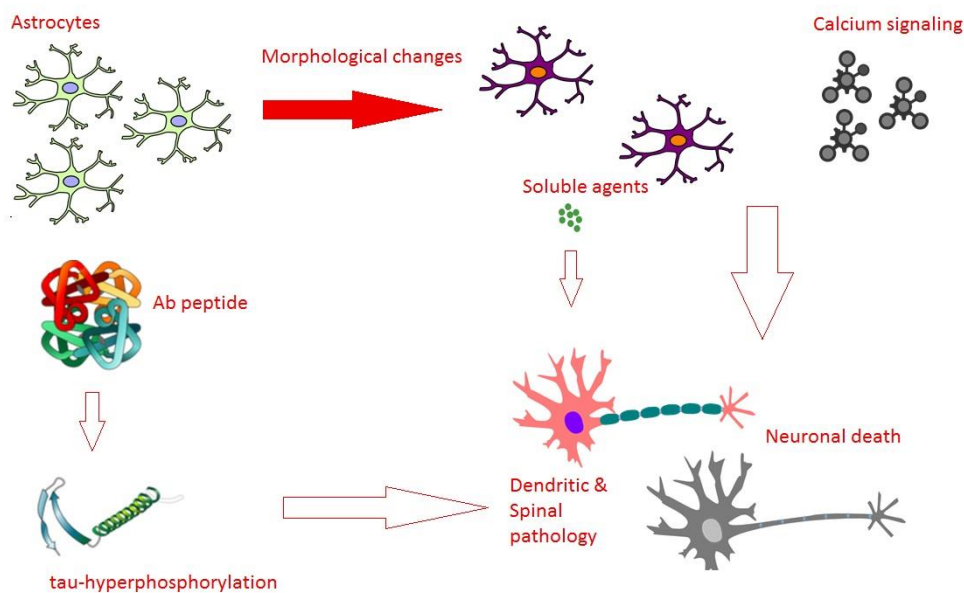


Figure 1. Schematic representation of the role of astrocytes in Alzheimer's disease.

Astrocytes and Ab clearance

Another controversial matter is the role of astroglial cells in processing and metabolism of Ab peptide. It has been suggested that reactive astrocytes in Alzheimer's disease participate in the clearance and degradation of amyloid [44, 45]. Activated astrocytes close to Ab plaques in the brains of transgenic APP mice express the amyloid-degrading enzyme, neprilysin [46], while in the entorhinal cortex of AD patients has been found accumulation of Ab peptide in astrocytes [47]. Further studies have demonstrated the ability of astrocytes of

phagocyte and degrade b-amyloid deposits in vitro, but this can only be done by astrocytes isolated from healthy brains and not from the APP transgenic mice [48]. Astrocytes produce the majority of apoE in the CNS, and previous evidence suggests that they are one of the main cell types in the brain that play a central role in the cellular clearance of A β [49-51]. Verghese et al (2013) presented evidence that do not support the existence of significant direct interactions of apoE isoforms with sA β in CNS fluids, and they suggested that the ability of apoE to influence Ab clearance or aggregation is mediated through its actions with LRP1 and other interacting receptors/transporters, marking the crucial role of astrocytes and other cells types in Ab clearance [52].

Furthermore, activated astrocytes surrounding Ab plaques were detected to express the endoprotease known as b-site APP-cleaving enzyme 1 (BACE-1), an enzyme required for the production of Ab, and in healthy brains is found only in neurons [44]. Moreover, many brain insults that trigger astrogliosis, have been also found to trigger the astrocytic expression of BACE-1 [53].

Astrocytes take up Ab through lipoprotein receptor-related protein 1 in the presence of amyloid-associated protein ApoE [54, 55]. Leucine-rich glioma inactivated protein 3, which co-localizes with Ab at the astrocytic cell membrane plays an important role in the internalization of Ab by astrocytes [56].

Formyl peptide receptors, a group of seven-transmembrane G protein-coupled receptors [57], which are expressed in neurons, astrocytes and microglia [54, 55], binds to Ab(1-42) and activates internalization of the complex Ab-FPRL 1 in microglia and astrocytes [60-64].

Toll-like receptors which are involved in the microglial clearance of monomeric, oligomeric and fibrillar Ab by microglia [63, 64], are also expressed in astrocytes [65 – 67].

Ab is rapidly trafficked to lysosomes after uptake and exogenous [68, 69], and degradation of Ab requires intact astrocytic lysosome function which is essential to prevent neurodegeneration [70]. Aging-induced impairment in lysosome function is thought to facilitates pathogenesis in AD [71], and enhancement of lysosomal biogenesis in astrocytes is highly efficacious in facilitating Ab and amyloid plaque elimination by them [72]. There is compelling evidence that A β pathology is closely associated with inflammation and reactive astrocytes and microglia are situated tightly around the plaques [73]. The formation of a glial capsule around the A β deposits may protect the surrounding brain tissue from toxic A β species, but the astrocytes and microglia have also been shown to secrete cytokines and neurotoxic products that could induce neuronal degeneration [74]. Astrocytes effectively engulf dead cells, synapses and protein aggregates of A β and α -synuclein [75-81]. Interestingly, astrocytes have been shown to be more efficient than microglia in taking up A β ,

particularly during the early stages of AD [82]. The fact that reactive astrocytes with high A β load are frequently found in the AD brain further confirms the importance of astrocytes in A β clearance [83]. Sollvander et al (2016) demonstrated that astrocytes engulf large amounts of protofibrillar A β ₄₂ which results in severe astrocytic endosome/lysosome defects and microvesicle-induced neurotoxicity. They concluded that accumulation of A β in astrocytes could play a vital role in the sporadic form of Alzheimer's disease [84].

Calcium signaling and Ab toxicity

Profound vascular pathology is another factor in AD physiopathology [68, 69 - 72, 85]. The neurovascular unit, which is the elementary component of microcirculation in the brain, integrate neurons, endothelium, pericytes and vascular smooth muscle [70, 71], with the role of astrocytes being the coordination of elements that establish the link between neuronal activity and blood flow [91, 92]. The astrocytic end-feet regulate the formation of tight junctions, controlling the transport of water and electrolytes, and providing neurons with energy substrates [88, 90]. CASR gene, a member of family C of the G-protein-coupled receptors which exhibits topological and sequence homology to the metabotropic glutamate receptors [93] and plays a role in the intracellular calcium concentration [94] form complexes with soluble or fibrillar Abs [91, 92]. CASR is expressing in every CNS cell type, including the astrocytes [92, 93] and seems to play a role in dendritic and axonal growth [93]. Oversecretion from the astrocytes' end-feet of an Ab.CaSR-mediated Vascular Endothelial Growth Factor -A, the surpluses of which are toxic to neurons, astrocytes and endothelial cells, resulting in blood-brain barrier functional impairment [94-97], has been noticed in the hippocampus of MCI stage patients [898]. Toxic Ab plaques seem to target the neurovascular units, affecting the microcirculation and vascular Ab clearance [57]. Furthermore, overproduction and release of VEGF-A is an atypical feature of AD. Ab.CaSR-induced signaling mechanism stimulates the secretion of neurotoxic Ab₄₂/Ab₄₂-os from human cortical postnatal neurons [92] and it is believed that plays a crucial role in the development of a vicious cycle of spreading Ab toxic elements within the brain [92, 99]. Amyloid beta enhances calcium signaling in astrocytes [58] and interacts with a number of surface receptors which leads to increase of intracellular calcium and disrupts gliotransmission [100, 101] with detrimental effects on neuronal homeostasis, synaptic transmission, and plasticity.

Discussions

For more than a century, the vast majority of research projects on the pathophysiology of Alzheimer's disease have been mainly focused on neurons, however increasing evidence comes to light showing the crucial role of astrocytes in cellular pathology, and Ab toxicity. Recent experimental evidence has shown that astrocytes undergo certain morphological changes when treated with Ab peptide, and they release soluble agents that mediate caspase-induced neuronal death [67-71, 85-87]. Furthermore, astrocytes are necessary for the Ab-induced tau phosphorylation, a critical event in AD pathophysiology [110].

Atrophy of astroglia which occurs at the early stages of AD is likely to accompany synaptic malfunction, synaptic loss, and cognitive deficits. Synaptic pathology is one of the early signs of brain pathology in AD and happens even before, or with poor correlation to Ab load and tangles expression, however, it is linked to cognitive decline [100 – 105]. Astrocytes, the fundamental elements of synaptogenesis and synaptic maintenance, control the composition of the extra-synaptic environment, preventing local glutamate toxicity and oxidative damage. In AD brains, astrocytes which are not in close proximity to senile plaques are atrophic, and therefore it is now accepted that they may a role in synaptic pathology.

Further studies are expected to be carried out in the near future on the role of astrocytes in AD and will definitely fill the gap in the knowledge of the precise etiological aspects of this disease which difficult the advance of therapeutics. Astrocytes are valuable novel therapeutic and neuroprotective targets for future treatments and mechanistic comprehension of AD.

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