Review Article

The role of Aquaporin 4 in Astrocytes is a Target for Therapy in Alzheimer's Disease

Abstract

Alzheimer's disease is a neurodegenerative disease characterized by deposition of extracellular amyloid-β, intracellular neurofibrillary tangles, and loss of cortical neurons. However, the mechanism underlying neuro degeneration in Alzheimer's disease (AD) remains to be explored. Many of the researches on AD have been primarily focused on neuronal changes. Current research, however, broadens to give emphasis on the importance of nonneuronal cells, such as astrocytes. Astrocytes play fundamental roles in several cerebral functions and their dysfunctions promote neurodegeneration and, eventually, retraction of neuronal synapses, which leads to cognitive deficits found in AD. Astrocytes become reactive as a result of deposition of Aβ, which in turn have detrimental consequences, including decreased glutamate uptake due to reduced expression of uptake transporters, altered energy metabolism, altered ion homeostasis (K+ and Ca+), increased tonic inhibition, and increased release of cytokines and inflammatory mediators. In this review, recent insights on the involvement of, tonic inhibition, astrocytic glutamate transporters and aquaporin in the pathogenesis of Alzheimer's disease are provided. Compounds which increase expression of GLT1 have showed efficacy for AD in preclinical studies. Tonic inhibition mediated by GABA could also be a promising target and drugs that block the GABA synthesizing enzyme, MAO-B, have shown efficacy. However, there are contradictory evidences on the role of AQP4 in AD.

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Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease clinically characterized by progressive deterioration of memory. In addition, histopathological changes such as deposition of extracellular amyloid-β (Aβ), intracellular neurofibrillary tangles (NFT) of hyper phosphorylated tau, and cortical neuron loss are widely noted. AD is the commonest form of dementia threatening 35.6 million people worldwide and this figure is expected to double every 20 years [1].

The exact mechanism behind AD development and progression is still unclear. Several hypotheses, however, have been proposed to address the pathological lesions and neuronal cytopathology of the disease. Of these hypotheses, the amyloid metabolic cascade and the intracellular neurofibrillary tangles are considered the most important hypotheses. However, many pharmacological treatments targeting at these and other hypotheses have been unsuccessful to delay the progress of the disease significantly [2]. This explains that no single theory alone is sufficient to explain the biochemical and pathological abnormalities of AD, which is believed to involve a multitude of cellular and biochemical changes.

AD is characterized by the involvement of different cell types including activated astrocytes and microglia, characterized by gliosis and neuroinflammation, which in turn contributes to the neuronal dysfunction and death observed in AD. Since AD pathologies are the result

of neuronal death, search for mechanisms and therapeutic approaches have been neurocentric till a recent time. However, the importance of nonneuronal cells, such as astrocytes, is now largely acknowledged and opened new research avenues that aim at better understanding of the pathology of the disease as well as characterizing new cellular and molecular targets for drug development. Thus the purpose of this review is to explore the role of reactive astrocytes in AD [3].

Astrocytes

Astrocytes are the most abundant cells in the brain and they can be broadly categorized into white matter astrocytes, gray matter astrocytes, ependymal astrocytes, radial glia, and perivascular astrocytes based on their anatomical location. Astrocytes play a fundamental role in several cerebral functions such as the development and maintenance of blood brain barrier, the promotion of neurovascular coupling, the attraction of cells through the release of chemokines, K^+ buffering, maintenance of general metabolism, control of the brain pH, uptake of glutamate and GABA by specific transporters, and production of antioxidants [4]. They are also involved in synaptogenesis and development of neuronal circuits by facilitating release of gliotransmitters. This shows the paramount role of astrocytes interaction with neurons in process and control of synaptic formation. Neuronal excitatory inputs activate astrocytes, which in turn mobilize $Ca2^+$ resulting in gliotransmitters release including glutamate into synaptic cleft. The released glutamate increases neuronal excitability and modulates synaptic function. In addition, astrocytes are involved in uptake of glutamate from synaptic space by excitatory amino acid transporter including GLT1. Once up taken, glutamate is metabolized into glutamine by glutamine synthetize before it is transferred to presynaptic neuron whereby glutamate and glutamine cycle is completed. This is very important means of maintaining hemostasis of glutamate in the tripartite synapse and preventing glutamate induced excitotoxicity. Astrocytes also regulate GABA level as they are endowed with enzymes responsible for GABA synthesis (GAD 67) and metabolism (GABA-T) [5]. It also expresses reuptake transporter protein called GABA transporter protein thereby regulating the level of GABA at synapse.

Astrocyte Reactivity

Astrocytic reactivity is functional and morphological change of astrocytes as a result of variety of brain insults and it is characterized by increased gene expression of a number of astrocyte structural proteins, such as glial fibrillary acid protein (GFAP) and vimentin; morphological changes, such as hypertrophy of the cell soma and processing; and proliferation, which is particularly important in the formation of an astrocyte scar around tissue lesions. It is usually implicated in several neurological disorders such as AD, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis [6]. Sustained reactive responses might be driven by positive feedback loops between microglia and astrocytes under conditions of severe and prolonged brain insults, thus providing detrimental signals that can compromise astrocytic and neuronal functions and lead to chronic neuroinflammation.

In patients with AD, reactive astrocytes are integral components of neuritic plaques and it seems to be particularly prominent around Aβ deposits both in the brain parenchyma and in the cerebrovasculature. However, their association with AD biomarkers and the functional impact of these cells and their therapeutic potential has remained elusive [7]. Recent advances in cell-type-specific gene delivery techniques have helped hugely to identify unique beneficial and detrimental roles of astrocytes in neurodegenerative disorders suggesting that astrocytic signaling cascades can be selectively exploited for treating AD. Detrimental effects of reactive astrocytes include altered glutamate homeostasis (decreased glutamate uptake due to reduced expression of uptake channel), altered energy metabolism, altered ion homeostasis (K^+ and Ca^+), increased glutamate, GABA, cytokines, and inflammatory mediator's release. Therefore, targeting specific astrocyte functions or specific aspects of reactive astrogliosis by targeting astrocyte-related molecular mechanisms is a viable option to counteract many CNS diseases [8]. In this review, the altered gliotransmitters release (tonic GABA inhibition), altered glutamate metabolism,

and aquaporins in reactive astrocytes as therapeutic target in Alzheimer disease are discussed.

Reactive Astrocytes as a Potential Target for Alzheimer's Disease

Glutamate, the major excitatory neurotransmitter, is carefully regulated by both neuronal and glial influences. Astrocyte transports the vast majority of extracellular glutamate via excitatory amino acid transporters. Of the five subtypes, EAAT2 is highly expressed throughout the brain and spinal cord and is responsible for more than 90% of total glutamate uptake. In astrocytes, glutamate is converted to glutamine by an enzyme glutamine synthetize which then is shuttled back to presynaptic terminals and is used for the synthesis of the neurotransmitter glutamate. This process is called glutamate–glutamine shuttle and helps for keeping glutamate hemostasis in the brain [9]. Astrocytes damage in a way that affects their ability to sense or respond to an increase in glutamate levels, therefore, disrupts the microenvironment nearby neurons and it causes overstimulation of the NMDA receptors, which are responsible for modulation of the cognitive functions in the frontal cortex [10].

Normal physiological aging process is associated with reduced NMDA receptors and their function is related to the physiological memory decline [11]. But these receptors, which are reduced in number and function due to aging, become overactive in certain regions of the brain (prefrontal cortex, hippocampus) in order to compensate for the memory loss which their continuous activation might trigger a glutamatergic cortical overactivation leading to excitotoxic damage of neurons. Accumulation of excess extracellular glutamate and subsequent overstimulation of glutamatergic NMDA receptors are thought to have numerous neurotoxic effects such as calcium homeostasis dysfunction, increased nitric oxide (NO) production, activation of proteases, increase in cytotoxic transcription factors, and increased free radicals [12,13].

Conclusion

Despite remarkable improvements in the understanding of the pathogenesis of AD, clear and accurate evidence on the mechanism of the disease is still lacking. Therapeutics so far targets majorly the hypothesis, excitotoxicity, and the cholinergic hypothesis and is symptomatic and hardly effective. However, the accumulating evidences on the importance of nonneuronal cells, such as astrocytes, opened new research avenues that aim at better understanding of the pathology of the disease as well as characterizing new cellular and molecular targets for drug development. The growing evidence on the physiological role of astrocytes in maintaining normal brain function shows that their altered functions due to reactivity play a key role in the etiology of AD and specific proteins such as MAO-B, the glutamate transporters, and AQP4 play key role in either protection or producing harmful effect and provide reliable targets for the pathogenesis of AD. According to current evidences, there are controversial findings on the role of reactive astrocytes in AD. Hence, further studies are warranted to fully characterize the effects of reactive astrocytes in AD and to search compounds which can modify their function.

References

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