International Research Journal of Biological Sciences ISSN 2278-3202
Vol. **12(3),** 17-20, November **(2023)** *Int. Res. J. Biological Sci.*

Review Paper

The Role of Astrocytes in Alzheimer's disease

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Available online at:www.isca.in, www.isca.me
Received 10th September 2023, revised 20th October 2023, accepted 9th November 2023

Abstract

Alzheimer's disease (AD) is a neurodegenerative condition that impairs cognition, causes memory loss, and alters a person's behaviour and personality. The deposit of amyloid-β (Aβ) plaques and hyperphosphorylated tau, which results in neurofibrillary tangles, in the brain are two important pathogenic characteristics of AD. Numerous investigations have determined and confirmed that astrocytes in AD have both neurotoxic and neuroprotective properties. The unique pathophysiological mechanisms and roles of these cells remain unknown despite several explanatory theories. The review outlines the neuroprotective roles of astrocytes, like as inflammation control and Aβ elimination. It concludes by highlighting the intricate interactions that exist between astrocyte activities and AD pathogenesis. Research on reactive astrocytes' balance between neuroprotection and neurotoxicity is still ongoing. Although there is now no treatment for AD, a better understanding of these pathways and therapeutic approaches that target astrocytes may be the key to developing more potent therapies for this debilitating illness.

Keywords: Astrocytes, Alzheimer's, Inflammation, Neurotoxic, Neuroprotective.

Introduction

Alzheimer's disease (AD) is a neuronal illness presenting with memory loss, cognitive decline, and behavioural and personality changes in those affected[1]. The disease manifests itself in two main forms: late onset (sporadic) and early onset (familial). Less than 5% of cases of AD are familial. Mutations in the three genes APP, PSEN1, and PSEN2 have been indicted in the causation of AD. Individuals above 65 years are at a higher risk of developing late-onset AD[2]. Increased levels of amyloid-β (Aβ) peptide, which are deposited extracellular in the brain as diffuse and neuritic plaques, and hyperphosphorylated tau (p-tau), a microtubule assembly protein that accumulates intracellularly as neurofibrillary tangles (NFTs), are the two main pathological changes seen in the brains of AD patients[3].

Pathophysiology of Alzheimer's disease

The main component of Aβ in AD is a peptide fragment that is created when the amyloid precursor protein (APP) is cleaved by the proteases β and γ secretases. During the early stages of the disease's pathogenesis, an imbalance between the synthesis and clearance of Aβ occurs, resulting in the development of Aβ plaques[4,5].

According to the amyloid hypothesis, the accumulation of Aβ in the brain tissues results in various other changes including development of neurofibrillary tangle, synaptotoxicity, mitochondrial dysfunction, neuroinflammation caused by aberrant activation of astrocytes and microglia, and neuronal death[6].

The central nervous system (CNS) resident microglia get activated when there is an excess of Aβ produced, which can be brought on by a pathogenic infection, inflammatory stimulus, or cellular debris. These microglial cells secrete proinflammatory cytokines like interleukin (IL)-1b, IL6, and tumour necrosis factor α (TNFα) and chemokines like chemokine (C-C motif) ligand (CCL) 2/4/11, which attract more microglia and astrocytes to the inflammatory region[7]. The recruitment of microglia and astrocytes into the inflammation site results in the overproduction of proinflammatory cytokines and chemokines, which ultimately fails to eliminate Aβ entirely. Degenerating neurons release chemical patterns and cell contents linked to injury, which exacerbate the inflammatory environment and lead to detrimental reactivity in microglia and astrocytic response[8].

Both the cholinergic and glutamatergic pathways participation in the aetiology of AD are supported by evidence, that patients with AD experience decreased concentration and functioning when acetylcholine (Ach), is necessary for processing memory and learning, reduced[9].

Glutamate is an excitatory neurotransmitter that plays a major role in memory, learning, and synaptic plasticity in the central nervous system. Excitotoxicity and neurodegeneration can result from activated microglia releasing an excessive amount of glutamate[10]. Increased glutamate levels can result from blocking of neuronal glutamate re-uptake at the synaptic cleft by the pathologically excessive amounts of Aβ present in the brain tissue in AD. An increase in glutamate would cause synaptic N-methyl-D-aspartate (NMDA) receptors to become more sensitive, which would lead to synaptic depression[11].

Overview of the Astrocytes

In the neural tissue of the CNS, the astrocytes are the glial cells that provide supportive function. Astrocytes are classified into two primary categories: fibrous and protoplasmic. The protoplasmic astrocytes are in every part of the grey matter, while the white matter contains fibrous astrocytes, which are identified by their several long processes that resemble fibres[12]. Through the astrocyte-neuron lactate shuttle, astrocytes play a major role in energy supply to neurons. Additionally, through the synthesis of gliotransmitters, they control Ca2+ fluctuations that affect neuronal activity[13]. Brain disorders like AD, Huntington's disease, ischemic stroke, and epilepsy are impacted by the regulation of astrocyte activity. In these conditions, astrocytes transform themselves to reactive astrocytes, which are further classified into A1 and A2 kinds[14].

The exact roles of astrocytes in AD varies depending on the stage of the disease and the specific microenvironment within the brain. Understanding the precise balance of astrocyte functions in AD and how to modulate these functions for therapeutic benefit remains an active area of research. Therapeutic strategies that target astrocytes are being explored as potential avenues for treating or slowing the progression of AD. Hence, we focused this review on the link between Astrocytes and AD.

Role of Astrocytes in Alzheimer's disease

Astrocytes oversee protecting the central nervous system from injury and repairing damaged neural tissue. The astrocytes accomplished this via a process called astrogliosis, during which the astrocytes alter in shape and molecular makeup in response to CNS injury. This process helps to produce a glial scar, which in turn promotes neuroprotection[15]. In response to damage, astrocytes release inflammatory mediators, which initates changes resulting in an astrocyte becoming reactive. Additionally, receptors such as Receptor for Advanced Glycation End Products (RAGE), which has two roles in the inflammatory response, are expressed by reactive astrocytes which surround Aβ. RAGE present on endothelial cells (ECs) or leukocytes can interact with its ligands in two ways: (i) first it can activate cells through the transcription factor NF-kappa B; (ii) second, RAGE on ECs can also act as an adhesive receptor that interacts directly with leukocyte ss2-integrins, which can directly contribute to the recruitment of inflammatory cells[16]. Additionally, astrocytes generate trophic chemicals that promote favourable activities in Alzheimer's disease (AD). Glial cell line-derived neurotrophic factor (GDNF) has been found to improve neural and cognitive performance in elderly rats. However, persistent inflammation caused by astrocytes is detrimental and can hasten the process of neurodegeneration[17].

Neurotoxic Reactive Astrocytes in Alzheimer's disease

A1 reactive astrocytes have been shown to be harmful and essential for neuronal death following acute CNS damage, LPS-induced neuroinflammation, and neurodegenerative diseases such as AD[18]. A1 reactive astrocytes are also neurotoxic because they upregulate a number of genes involved in the classical complement cascade, which have been shown to be detrimental to neuronal synapses. On the other hand, ischemia induces A2 reactive astrocytes, which strongly upregulate a variety of neurotrophic factors for tissue repair and neuronal survival[19]. Activated microglia produce TNFα, C1q, and Il-1α, which in turn trigger the formation of A1 reactive astrocytes. It has been observed that 60% of AD patients have A1 reactive astrocytes, which secrete a neurotoxin that causes fast neurodegeneration, which accelerates the course of illness[20].

Neuroprotective role of astrocytes in Alzheimer's disease

Various research studies are being conducted to recognise the neuroprotective role of astrocytes in AD, and the precise mechanisms and contributions of these cells. A key component of AD pathogenesis, which is the elimination of abnormally accumulated Aβ, is facilitated by astrocytes. They can absorb and break down Aβ, which lessens its accumulation in the brain[21]. An excessive accumulation of Aβ can result from a dysfunction in this clearance process, which adds to the neurotoxicity associated with AD. Chronic neuroinflammation is a major characteristic of AD, and astrocytes can either stimulate or inhibit inflammation. They can release anti-inflammatory chemicals when they're in a healthy state, but they can also become activated in AD and release pro-inflammatory cytokines. It may be possible to prevent the damage to neurons by altering these reactions[22].

BDNF are produced and released by astrocytes which aid in the survival, growth, and function of neurons. These elements might aid in reversing the neurodegenerative processes in AD.

Controlling the flow of chemicals from the circulation to the brain is performed by the blood brain barrier (BBB). Astrocytes are necessary to keep the integrity of the BBB intact. When the BBB fails, then dangerous chemicals may penetrate the brain tissue and exacerbate the pathogenesis process of AD[23].

To precisely understand how astrocytes impact AD pathogenesis and to create therapeutic approaches that makes use of their neuroprotective properties in the setting of AD, needs more investigation.

Astrocytes have a role in the production of amyloid

The BACE1, γ-secretase, and amyloid precursor protein (APP) are three essential components required for the synthesis of amyloid. Because of neuroinflammation brought on by AD, reactive astrocytes express more APP than they do while at rest, which in turn increases the production of Aβ. This has been demonstrated by a study that shows that in primary mouse astrocytes, activation with a proinflammatory cytokines (TNFα + IFNγ, and IL-1β) increases the production of APP. Furthermore, it has been discovered that a mix of TNFα and IFNγ can increase the expression of Aβ in a human astrocyte[24]. In a healthy brain, BACE1 is mostly expressed in the neurons. Nonetheless, prior studies have demonstrated that reactive astrocytes from Alzheimer's patients express BACE1. IFNγ and TNFα upregulate BACE1 expression in astrocytes, which raises total amyloid burden in a manner like that of APP expression[25].

Stressors that are specific to cells can also activate BACE1 and APP, which in turn cause astrocyte Aβ production in addition to neuroinflammation. For example, the stimulation of the hypothalamic-pituitary-adrenal axis results in the adrenal cortex releasing glucocorticoids, which in turn increase the expression of BACE1 and APP. Furthermore, astrocytes may express APP because of tissue injury[26].

In summary, this indicates that a feed-forward mechanism is present the pathogenesis of AD. Amyloid beta causes microglia and astrocytes to release more proinflammatory cytokines, which raises the production of APP and BACE1, maybe also increase γ-secretase activity to boost astrocytic Aβ secretion. This Aβ leads to increased neuroinflammation and subsequent amyloidosis.

Conclusion

Alzheimer's disease (AD) is a widespread and debilitating progressive neurodegenerative condition that act on people. It is characterised by the destruction of neurons of brain, which impairs cognitive ability and independence in day-to-day activities. As discussed in this paper, several recent research have provided fresh perspectives on the pathophysiology and astrocyte-related mechanisms of AD, though there have been some discussion and disagreement over the function of astrocytes. However, several investigations have identified and validated both the neuroprotective and neurotoxic processes of astrocytes. Despite the abundance of explanatory theories, the precise pathophysiological mechanisms remain unknown. AD currently has no known cure, yet there are therapies that reduces its symptoms. Therefore, more research is required to study the processes governing the balance between the neurotoxic and neuroprotective effects of reactive astrocytes which will be crucial in understanding their activities, based on which effective treatments for AD can be developed.

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