Neuroinflammation in Alzheimer's Disease: Current Therapeutic Approaches and Recent Progress

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Abstract

Alzheimer's Disease (AD) is a progressive neurological disorder, characterized by amyloid-beta (Aβ) and neurofibrillary tangles (NFTs). Recently a new factor called neuroinflammation is added which can directly play a key role in the progression of AD. The recent studies in humans and mice had shown that aggregated protein (Aβ and NFTs) binds to the microglia cells (the resident innate immune cells) found in the central nervous system and activates the innate immune response which is characterized by the release of inflammatory mediators and increase the disease progression through the neuroinflammation. Several factors such as traumatic brain injury, obesity, etc. can play a major role in neuroinflammation. Hence targeting the immune mechanism and reduce the risk factors could lead to future promising therapeutics for AD.

Keywords: Alzheimer's Disease; Neurofibrillary Tangles; Drug Development; Microglia; Neuroinflammation

Introduction

In the first glimpse, immunology and neurobiology are not very much different. Based on the cellular perspective, the brain represents the stasis mechanism while the motion mechanism is represented by the immune system. We can combine these two mechanisms to understand neurodegenerative diseases such as AD, Parkinson's disease, etc. The recent evidence suggested that inflammation is playing a key role in disease progression. Hence understanding the mechanism of the nervous system and immune system interaction can prevent or hinder the progression of CNS diseases. In AD, the neuroinflammation is not only activated by the Aβ and NFTs formation however it also participates in the disease pathogenesis even more than Aβ and NFTs [1]. Several key genes like TREM2 [2] and CD33 [3] play a key role in the neuroinflammation induced AD progression. The analysis of several stages of dementia such as mild cognitive impairment showed the early and significant participation of inflammation in the AD progression [4]. In this review, we will describe the various cell types which are involved in neuroinflammation along with the therapeutic approaches and ongoing clinical trials against AD neuroinflammation.

Neuroinflammation in Alzheimer's Disease

Other than two major hallmarks such as Aβ and NFTs in AD, neuroinflammation is the third core neuropathological feature [5]. Around the NFTs and plaques, the activated astrocytes and microglia cells are also found. In AD brains the inflammatory markers or pro-inflammatory cytokines level is also increased [6]. This evidence of inflammatory reactions suggests the response of the immune system against the Aβ and NFTs deposition [7]. Ultimately the neuronal damage or neuron cell death happens due to the uncontrolled activation of these inflammatory processes through microglia and other cells which is very harmful and increases the AD progression [8] (Figure 1). In this section, we will discuss the different type of cells which participates in the neuroinflammation mechanism.
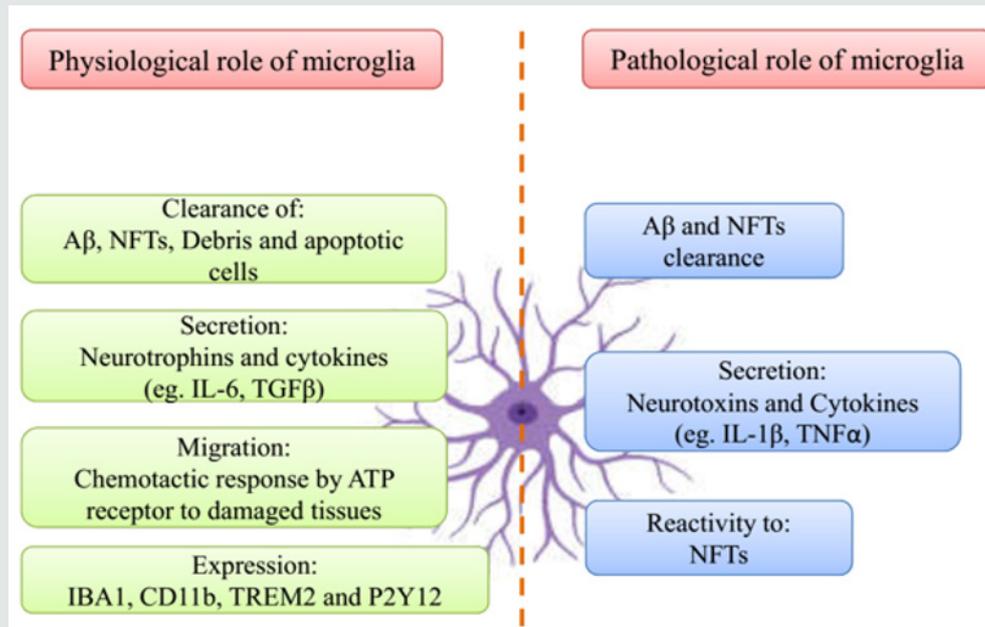
Figure 1: The difference in the microglia functions under physiological and pathological conditions.

Microglia

Microglia is a type of resident immune cells located in the central nervous system (CNS). They perform several functions such as antigen-presenting, phagocytosis, and produce immune mediators like peripheral monocytes. The microglia cells interact with the Aβ and NFTs with the help of G-protein coupled receptors (CMKLR1 and FPR2), TERM2, scavenger receptors (MARCO, CD36, SCARA-1, SCARB-1, and RAGE), toll-like receptors (TLR9, TLR6, TLR4, and TLR2), CD47 and α6β1 integrin [9]. The microglia cells are activated by using the NF-κB pathway after the initial recognition [10]. Due to the constant presence of the senile plaques and Aβ, the microglia cells are continuously activated. Due to the pro-inflammatory mediators which are produced by Aβ due to the chronically activated microglia, the phagocytosis ability is decreased, and which results in prolonged neuroinflammation in AD [11].

Astrocytes

Astrocytes are also a type of glial cells that participates in the waste clearance, nutritional supplementation to neurons, and maintenance of the blood-brain barrier. The increasing glial fibrillary acidic protein (GFAP) indicates astrocyte activation [12], astrogliosis, and astrocyte atrophy [13] which happens before the AD even before the Aβ and NFTs formation. The astrocytes can also be activated by the NF-κB pathway [14]. In some cases, these activated astrocytes destruct the Aβ itself, and use the ApoE lipidation [15] to increase the phagocytosis of microglia. Although these activated astrocytes increase the neuroinflammation through the inflammatory mediators [16].

The oligodendrocytes are the key resource of the myelin in the central nervous system,. The oligodendrocytes role in AD is still a mystery and scientists are working on it. A recent study showed that oligodendrocytes can contribute towards the neuroinflammation process because they can do the complement system synthesis [17].

Cytokines

In AD, cytokines play a diverse role in neuroinflammation. The production of Aβ is increased through the TNF-α by β- and γ-secretase through the amyloid precursor protein (APP) [18]. The same function (generation of Aβ) is performed by IL-1 also [18]. By using the p38-MAPK pathway the tau protein phosphorylation is also increased by the IL-1 [19]. The IL-6 also increases the tau protein phosphorylation by using the cdk5/p35 pathway [20] along with the higher expression of APP [21]. In the CNS, the microglial migration is regulated by chemokines. In the human mononuclear cells, the Aβ increased the production of CCL2, CCL3, CCL4, and CXCR8 [22]. For the synapse maturation, function and for maintaining the microglial resting-state maintenance the CX3CR1/CX3CL1 play an important role [23]. The CX3CR1/CX3CL1 is responsible for the cognitive decline and amyloid deposition is shown in an animal model recently [24]. The neurons, astrocytes, microglia, and oligodendrocytes produce the components of the complement system in the CNS [25]. The role of the complement system in AD is still unexplored very well. Due to the interaction of C1q with the Aβ, the alternate complement pathway is activated, and it induces the neuroinflammation and phagocytosis of Aβ [26]. The C3 deficiency is associated with amyloid phagocytosis and higher Aβ accumulation in an animal model. Association between

the complement inhibitor, apolipoprotein J, and complement receptor 1 indicates the potential role of the complement system to AD in a genome-wide association study [27].

5. Potential Therapeutics for Neuroinflammation in AD

The current treatment of AD can provide only symptomatic relaxation instead of a permanent cure. There are two types of medications available to treat AD. First are the cholinesterase inhibitors (rivastigmine, donepezil, and galantamine) and second are the NMDA inhibitors such as memantine. There is an urgent need to find an alternate therapeutic approach due to the higher failure rate in AD drug discovery [28]. Hence targeting the neuroinflammation mechanism by using several therapeutic strategies can be beneficial for AD management.

Several approaches are developed such as inhibiting cytokines release, reducing cytokines gene expression, and preventing cytokines binding to their receptors [29]. The minocycline is a type of anti-inflammatory molecule shown a reduction in the release of the cytokines from the astrocytes and hence it showed the benefits in the cognitive deficits in AD mouse models [30,31]. In another study, it was found that inhibition of tau phosphorylation kinases can also give the suitable results of modulating neuroinflammation in animal models [32]. The reduction in oxidative injury also showed a promising result. Like inducible nitric oxide synthase and cyclooxygenase-2 inhibition showed good results in the *in vitro* and in vivo animal studies [33]. Although the Dimebon (latrepirdine) acts as a mitochondrial enhancer and failed in a clinical trial (NCT 00912288) [34]. It showed that more efforts should be made to find the therapeutics for restoring the mitochondrial dysfunction which can help in the synaptic and neuronal function restore mechanism [35].

In other approaches, the microglial function is targeted through experimental manipulations to reduce the axonal dystrophy and increase the microglial encapsulation of amyloid plaques [36]. The recent studies showed that anti-Aβ antibody [36] or anti-ApoE antibody passive immunization promotes the microglia recruitment in the region of amyloid plaques in AD mouse models. It is shown that knockout of CX3CR1 (chemokine receptor) in microglia can reduce the plaque burden [37] by increasing the formation of microglial barrier in the region of amyloid plaques [36]. The small molecules such as AZD8797 [38] and CX3CR1 and its receptor targeting antibody can also neutralize the CX3CR1 function. Although the CX3CR1 cannot target without concerns [39].

There are many other mechanisms by which the inhibitors or modulator can be designed. Several clinical trial studies are going on to find the potential inhibitor against AD [40] and we have summarized a few of them in (Table 1).

Table 1: The table describes the different type of neuroinflammatory drugs which are in the clinical trial.

Drug name	Clinical trial No.	Clinical trial phase	Description	Status
Tarenflurbil	NCT00380276	III	non-steroidal anti-inflammatory drugs (NSAIDs)	Terminated
	NCT00322036			
Celecoxib	NCT00007189	III	NSAIDs	Completed
Ibuprofen	NCT02547818	III	NSAIDs	Active, not recruiting
Salsalate	NCT03277573	I	NSAIDs	Active, not recruiting
Pioglitazone	NCT01931566	III	Acts as an agonist of Peroxisome-proliferator activated receptor γ (PPARγ)	Terminated
	NCT02284906			
Resveratrol	NCT01504854	II	Phenol, antioxidant	Completed
	NCT01716637			
	NCT00678431			
Azeliragon (TTP488)	NCT02080364	III	Inhibitor of receptor for advanced glycation end products	Terminated
	NCT02916056			
Etanercept	NCT01068353	I/II	Tumor necrosis factor-alpha (TNF-α) inhibitor	Completed
	NCT01716637			
Neflamapimod (VX-745)	NCT03435861	II	selective inhibitor of p38 mitogen-activated	Recruiting
	NCT03402659		serine/threonine-protein kinase p38 MAPK (p38 MAPKα)	Completed
Simvastatin	NCT00939822	II	3-hydroxy-3-methyl-glutarylcoenzyme A (HMG-CoA) reductase inhibitor, cholesterol targeting	Active, not recruiting
Dimebon	NCT00912288	III	Blocks the H1 histamine receptors	Terminated
Valacyclovir	NCT03282916	II	Inhibit the Herpes simplex virus-mediated neuroinflammation	Recruiting

Conclusion and Future Perspective

AD is a complex, multifactorial disease and cannot be explained by only one hypothesis. On dated 22/11/2020, the 2453 clinical trials are listed on the clinicaltrials.gov website for AD including drugs, therapies, and imaging markers. To date, there is no drug that can completely cure AD due to the higher failure rate in the late clinical trials. Lesions from the previously failed clinical trials suggest that the pathophysiological mechanisms are not only limited to the amyloid and tau hypotheses while other mechanisms such as neuroinflammation and others are also involved in the disease pathology progression. The CNS innate immune response triggered neuroinflammation plays a key role in the disease pathogenesis. Additionally, neuroinflammation is an early cause of AD instead of a late consequence of AD. Due to the key role of neuroinflammation in AD the anti-inflammatory therapeutic development which can improve the function of microglia can be a promising therapeutic strategy to alter the progression of AD. We believe that the drugs which can act as the anti-inflammatory agent can be beneficial for AD and several other neurodegenerative diseases.

Acknowledgement

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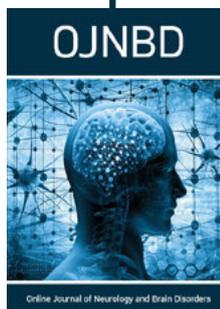
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