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Review

Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss and dementia. The pathological characteristics of AD include the deposition of amyloid beta (Aβ), neurofibrillary tangles, and neuronal loss. There is evidence showing the involvement of inflammation in AD, including activated microglia within and surrounding senile plaques. Epidemiological studies suggest the use of anti-inflammatory drugs to reduce incidence of AD. However, clinical trials with anti-inflammatory drugs have not been successful.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and one of the leading causes of morbidity and mortality in the aging population. AD patients suffer from a decline in memory, aphasia, performance disorders, personality and behavior changes and eating problems and infections in advanced dementia. These symptoms lead to the decline of patients' life quality and increase cost of care which will be important public health challenges [1–8].

AD begins with subtle and poorly recognized failure of memory which is often called mild cognitive impairment and slowly becomes more severe and incapacitating at the late stages [5,8]. There is a long pre-symptomatic period between the onset of pathological changes in the brain and the development of clinical symptoms of AD. Owing to very long-lasting early stages of AD, intensive research is undergoing to identify diagnostic biomarkers and treatment options for the prevention of disease [2,8].

AD is a complex multifactorial disease with many contributing factors. Essential neuropathologic changes and the main features of AD include; extracellular plaques containing amyloid beta (Aβ) and intracellular neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein, along with synaptic and neuronal losses (5). Amyloid precursor protein (APP) is a transmembrane protein which is fragmented by proteases named α, β, and γ -secretase. Aβ is non-soluble and neurotoxic which is derived from APP via beta-secretase and gamma secretase enzymes successively and aggregates in brain tissue. In AD, inefficient clearance of Aβ is the major pathogenic pathway due to the insufficient microglial phagocytic capacity as a result of increased cytokine levels and downregulated Aβ phagocytosis receptors (7). NFT arises from hyperphosphorylation of tau protein [1–3,8]. In addition to these essential features, several other pathologic changes such as inflammation, sustained activation of microglia and other immune cells are commonly observed in association with AD. In recent years increasing evidence suggests that inflammation has a significant role in AD pathogenesis, however, little is known about the exact contribution [3–8]. It has been demonstrated that Aβ activates microglia causing release of proinflammatory cytokines. These cytokines induce production of APP and due to increased amount of APP, production of Aβ becomes higher [1,9,10].

Genome wide association studies indicated that several genes (TREM2, CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP) related with an increased AD risk regulate glial clearance of misfolded proteins and inflammatory reaction. APOEε4 is the most accepted gene that has been associated with an increased risk for AD reported in many studies [11,12].

It has been observed that permeability of immune cells and molecules through blood-brain barrier (BBB) increases with aging which leads neurodegeneration in AD [2]. Although some AD cases are genetically linked, there are many diseases and lifestyle factors that can lead to an increased risk of developing AD, including traumatic brain injury, diabetes, hypertension, obesity, and other metabolic syndromes, in addition to aging. Identifying common factors in these conditions causing AD could enhance our understanding and help to the development of more effective treatments for AD [2].

There is a great need to develop therapies to prevent AD and/or to slow its progression. It is not easy to develop effective drugs because the

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mechanisms underlying AD pathogenesis have not been clarified fully. Since it is considered as a mutifactorial disease, therapies should involve multiple disease targets instead of a single drug therapy.

2. Inflammation in Alzheimer's disease

Inflammation is another underlying mechanism of AD pathophysiology in addition to Aβ and NFT. Although the relation between AD and neuroinflammation was discovered more than 30 years ago, it is still not clear if it is a cause or consequence of the disease [4,19]. Inflammation usually resolves itself and is essential for the repair process. However, if inflammation is prolonged, it becomes chronic inflammation which can cause detrimental effects on brain functions due to excessive or persistent release of cytotoxic factors. The persistent overactivation of pro-inflammatory responses has been implicated in many neurodegenerative disorders including AD [4].

There is a large amount of evidence demonstrating involvement of neuroinflammation in AD pathogenesis [6]. Microglia and astrocytes are the major source of cytokines in AD. Cytokines contribute to the development of neuroinflammation [7]. Microglia are the resident immune cells of the CNS. They play a fundamental role in brain surveillance and homeostasis [4]. Microglia may have beneficial and detrimental roles and effects [7]. Under physiological conditions, microglia are neuroprotective, play a key role in phagocytosis and neurotrophin release, their function is to maintain a healthy brain environment. However, in response to disease, inflammation or injury, microglia become activated, leading to the production and release of inflammatory cytokines, including interleukin-1α (IL-1α), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) or reactive oxygen and nitrogen species resulting in a pro-inflammatory response. During presymptomatic stage of AD, microglia is activated by proinflammatory mediators, leading to synaptic dysfunction and neuronal death [6]. Activated microglia synthesize proteolytic enzymes such as Cathepsin B which damage extracellular matrix and cause neuronal dysfunction [4]. Increased microglial activation and cytokine expression in AD have been observed in several studies [1,3]. It has been demonstrated that Aβ activates complement system and microglia which cause release of anaphylatoxins, and proinflammatory cytokines promoting inflammation further. The cytokines induce production of APP and due to increased amount of APP, production of Aβ becomes also higher [1,9,10]. Activated microglia have been shown to produce free radicals, nitric oxide and neurotoxic substances which kill neurons in cell culture studies [5,6]. T cells are activated in brain parenchyma in AD which release inflammatory cytokines such as IL-1, IL-6, TNF-α, and γ-interferon [19]. The presence of activated microglia surrounding amyloid plaques and increased levels of proinflammatory cytokines in both the periphery and central nervous system (CNS) support the key role of inflammation in AD [4].

Unlike other risk factors and genetic causes of AD, neuroinflammation is not typically the cause, but rather a result of AD pathologies or risk factors associated with AD and increases the severity of the disease by exacerbating Aβ and tau pathologies [3]. Neuroinflammation is a major field of brain research today. Inhibition of neuroinflammation might be a good treatment modality in many chronic neurological disorders including AD.

In spite of strong evidence that inflammation plays an important role in AD pathogenesis, the detection of inflammatory markers has not yet been established as valuable tool for the diagnosis or monitoring of AD. The results of studies on neuroinflammatory markers in the CSF are often controversial due to different sampling times and disease stages [7]. Blood-based biomarkers identified by proteomic methods are cytokines and brain-derived neurotrophic factors. Recently developed positron emission tomography (PET) imaging agents targeting neuroinflammatory processes offer the possibility to in vivo track diverse brain inflammatory events. Specifically, neuroinflammatory events such as microglial activation, reactive astrocytes, and increased phospholipase activity can be quantified by using PET radiotracers [4,5].

3. Anti-inflammatory treatment options for Alzheimer's disease

There is no fully effective cure for AD yet. Recent failures of several AD clinical trials have demonstrated that when AD progresses to an advanced degree, excessive neurodegeneration becomes irreversible and aberrant neural networks cannot be repaired with treatments to reduce amyloid accumulation or oxidative stress. Therefore, current treatment efforts have been shifted to AD prevention in the early stages of disease [1–7]. There are a few treatment options available that may improve some symptoms. Currently, two classes of drugs—cholinesterase inhibitors (i.e., donepezil, galantamine and rivastigmine) and *N*-methyl-D-aspartate (NMDA) receptor antagonists (i.e., memantine)—are approved for the treatment of AD. In AD, cerebral choline acetyl transferase is reduced which leads to a decrease in acetylcholine synthesis and cortical cholinergic dysfunction. Cholinesterase inhibitors such as rivastigmine, donepezil and galantamine increase cholinergic transmission and provide modest symptomatic benefit. Memantine is an NMDA receptor antagonist which inhibits excessive NMDA stimulation activated by high glutamate released in patients with AD. No new drug has been approved since Namenda (memantine) in 2003, despite the extensive number of clinical trials [2,6,8].

Restoring the physiological function of microglia and astrocytes might be a new treatment modality for AD therapy. Different strategies are developed to modulate immune cell function in neuroinflammation such as reducing expression of cytokines, inhibiting cytokine release and preventing cytokines to bind to their receptors. Reducing oxidative injury via inhibition of cyclooxygenase-2 and inducible nitric oxide synthase has been shown to have neuroprotective effects in vitro and in vivo animal studies. Recruitment of microglia around amyloid plaques and promoting microglial encapsulation of amyloid plaques, formation of microglial barrier around amyloid plaques to reduce plaque load have been tried in experimental animal models with promising results [6].

In the past three decades, several epidemiological studies demonstrated that individuals can be spared from AD if they have been taking non-steroidal anti-inflammatory drugs (NSAIDs) [19]. There are more than 20 different NSAIDs available commercially. They are used in multiple medical conditions for anti-inflammatory, analgesic and antipyretic purposes. There is controversial data for showing evidence that NSAIDs reduce the risk of AD or not. The incidence of AD was found lower in patients with rheumatoid arthritis with long-term NSAIDs medication [1,3,13].

Four large epidemiological studies analyzed the effects of NSAIDs on AD and showed the sparing effect ranging between 36% and 80%. Some NSAIDs at very high doses bind to Aβ directly, but they were not more effective than other NSAIDs in reducing the risk of AD [18,19].

One large epidemiological study (The Baltimore longitudinal study) showed a sparing effect of 60% among aspirin and NSAIDs users for two or more years [14]. Another study demonstrated a 55% reduced risk of AD with NSAIDs usage and found higher reduction with increased duration of medication (the Cache County study) [15]. The Rotterdam study showed an 80% sparing [19,20]; and the MIRAGE study showed a sparing of 36% [19,21].

In contrast to these trials, a large randomized trial investigated the efficacy of naproxen and celecoxib in the prevention of AD in individuals over 70 years with a history of at least one family member with AD demonstrated that AD risk was actually increased in both active treatment groups. The trial was stopped early because of an increased risk of cardiac diseases in patients treated with naproxen [16].

Another large randomized study of 3350 participants over 50 years found that low dose aspirin medication failed to show improvement in cognitive performance after 5 years [17].

Some NSAIDs including diclofenac, flurbiprofen, ibuprofen, indomethacin, piroxicam, fenoprofen, diflunisal, meclofenamate, and sulindac have an effect of γ-secretase modulation shifting Aβ production from the aggregable form (Aβ42) to a more soluble form (Aβ38) and defined as selective $A\beta_{42}$-lowering agents (SALAs). A literature review of SALAs showed no difference for reduction of AD risk compared to other NSAIDs [18].

According to the treatment guidelines, there is no recommendations for NSAIDs to be used for preventing dementia, and with the potential harms, they should not be used for the treatment or prevention of dementia or cognitive impairment.

In a recent review published by Zhu et al [1]. specialized pro-resolving lipid mediators (SPMs) which are the downstream products of omega-3 fatty acids, have been proposed as effective agents resolving inflammation. It was shown that SPMs can improve neuronal survival and increase microglial phagocytosis of Aβ in in vitro studies, indicating that stimulating resolution of inflammation may be a potential therapeutic target in AD. No side effects of SPMs have been reported so far, but before their use on patients with AD, there must be further evidence for their safety and for their ability to pass the BBB. It should be also investigated if stimulating pro-resolving activities can initiate repair and neuronal regeneration in AD involving chronic inflammation [1].

Since AD is a multifactorial disease, AD therapy has been shifted from single target approach (primarily amyloid-centric) to developing drugs targeted at multiple disease aspects, and from treating AD at later stages of disease progression to focusing on preventive strategies at early stages of disease development covering symptomatic treatments, lifestyle modifications and risk factor management [6]. Modulation of risk factors and intervention with immune mechanisms are likely to lead to future preventive or therapeutic strategies for AD [7].

4. Conclusion

This brief review highlights the AD pathogenesis and novel therapeutic targets for treatment of AD. Further studies are needed to find a way for more appropriate therapy for resolving the disease progression including chronic neuroinflammation with appropriate timing. Therefore, tools such as immuno-based biomarkers and imaging technics for disease at preclinical stages are required. Elucidating the contributions of microglia, macrophages, astrocytes, neurons and endothelial cells to neuroinflammation and inflammatory biomarkers in the CSF, peripheral blood or in the brain by imaging at different stages of AD should be the focus of future studies.

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