Dean&Francis
ISSN 2959-409X

Neuroinflammation Hypothesis and Alzheimer's Disease

Chuci Wang[1, *]

[1]Northeast Yucai School, Shenyang, China

*Corresponding author: s1322831@live.hkmu.edu.hk

Abstract:

A serious, long-term degenerative neurological disease in humans is one definition of Alzheimer's disease (AD). AD brain areas that are pathologically sensitive exhibit inflammation, and this inflammation carries with it all the complexity of peripheral local inflammatory responses. Degenerating tissue and the buildup of very insoluble aberrant materials are two traditional causes of peripheral inflammation. Nowadays, the inhibitors which were discovered before cannot have a good effect on the treatment to the growth of this disease. This article provides an overview of how microglia-mediated neuroinflammation affects AD, with particular attention to the pathogenic process of microglia, and the potential and recent developments in neuroinflammation as an AD diagnostic and treatment target. Therefore, even if clinical research and animal models are still in their infancy, they clearly imply that AD inflammation plays a major role in AD pathogenesis. Gaining more insight into the immunoregulatory and inflammatory mechanisms underlying AD should make it feasible to create anti-inflammatory treatments that, while probably not curative, will at least assist postpone the start or decrease the disease's terrible course.

Keywords: Alzheimer's disease, neuroinflammation, microglia, treatment.

1. Introduction

Two basic theories are responsible for the development of AD, one kind of dementia which are proposed before the hyperphosphorylated tau protein and amyloid plaque, which is prevalent worldwide. These two disorders are the direct results of senile plaque (SP) and Neurofibrillary tangles (NFT). The "amyloid cascade hypothesis," regarded as the most widely accepted biological mechanism of AD development, while AD does not develop when adding Aβ to the brains of healthy mice or people who are healthy. In addition, the medical circumstances of AD patients could not be improved by removing Aβ from their brains. Therefore, this hypothesis still lacks sufficient evidence to support it, and research on the pathogenesis of AD needs to continue in order to find new targets for treatment [1].

At present, more and more research is being done on neuroinflammation as a possible treatment target

ISSN 2959-409X

for AD [2]. Over forty loci have been identified as target genes associated with late-onset AD (LOAD) [3], with glial cells housing a large number of these genes, especially, microglia have been the major topic in the research which are naturally occurring immune cells within the CNS, constituting 5-10% of total CNS cells [4]. Nowadays, there are several drugs invented in order to prevent neuroinflammation. As an off-label tactic, some previously approved medications were also being evaluated for AD. In preclinical research, the calcium channel blocker antihypertensive medication nilvadipine showed anti-inflammatory and anti-tau efficacy in addition to reducing the generation of amyloid and increasing cerebral blood flow [5].

However, when a prolonged injury goes untreated, these responses can initially be neuroprotective but frequently end in detrimental, chronic neuroinflammation later on due to microglia that emit excessive amounts of pro-inflammatory proteins [2]. This review focuses on the mechanism of the neuroinflammatory hypothesis and This highlights the potential of targeting microglia and neuroinflammation as therapeutic and diagnostic approaches for the treatment of Alzheimer's disease.

2. The Hypothesis of Neuroinflammation

Two types of neuropathologic changes that linked to Alzheimer's disease are: (1) positive lesions which are characterized by accumulating neuropil filaments, dystrophic neurites, amyloid plaques, NFTs, and other brain debris in people with AD. These changes provide insight into the progression of the disease and its associated symptoms. Additionally, two negative lesions, induced by neuronal loss, exhibit substantial atrophy due to the depletion of neurons, neuropils, and synapses. Furthermore, neurodegeneration may also be caused by other factors, including oxidative stress, neuroinflammation, and damage to cholinic neurons [6].

2.1 The Mechanism

When pathological lesions occurs in the peripheral nervous system or the central nervous system, the brain responds by becoming inflamed. This process results in the production of various proinflammatory cytokines, including IL-6, IL-1β, IL-8, TNF and chemokines and cytokines of the complement system. Additionally, small molecule signaling molecules, such as prostaglandins and nitric oxide (NO), and reactive oxygen species (ROS) [3]. The brain's acute infection often serves as the body's defense against stimuli, infections, and injury to the nervous system. On the other hand, chronic inflammation develops from acute inflammation over time in order to activate the neurological system. due to chronic inflammation may be released, exacerbating the inflammation, damaging neurons, and resulting in a variety of pathological changes in the body [7]. Particularly during inflammation, body's own bioactive lipids control a wide range of cellular and molecular processes associated with both health and illness. All major endogenous bioactive lipids have close connection with chronic inflammation such as AD. Since microglia produce and express more inflammatory cytokines than other glial cells do, it is thought that microglia are the most important cause of inflammation in the brain. Furthermore, because of their many phenotypes, microglia have drawn the interest of medical experts more and more. Furthermore, microglia are linked to memory impairment, tau phosphorylation, and synaptic loss, which makes these biological processes the focus of growing amounts of research on neuroinflammation in AD [3].

2.2 Microglia

Microglia, which began as mesoderm and moved to CNS throughout development, are CNS resident macrophages [8]. Microglia has essential effect of protection in CNS physiological processes and are thought to be a crucial defense to preserve equilibrium, serving as the body's first line of defense is the innate immune system, regulating the quantity of neurons within the CNS. Through brain-derived neurotrophic factor signaling, microglia support neuronal survival and differentiation during bodily development. They also play a role in the creation of learning-related synapses.

2.2.1 The Biomarkers

According to certain theories, microglia are important in AD, and the overexpression of a particular biomarker for microglia suggests that an increase in microglia may cause cognitive impairment [9]. An important channel for communication between neurons and microglia is formed by IBA-1 and the fractalkine receptor CX3CR1, which is found on both microglial cells and on the microglial and neuronal ligand CX3CL1 receptors [10]. The brain of people with AD have been found to have microglia associated with Aβ plaque. Activated microglia in AD are characterized by increased proliferation including CD14, CD11c, MHC-II, and iNOS, and M1 phenotype markers (MCP-1, IL-6, MIP-1, IL-1, and TNF) and chemokine receptors. (e.g. CCR3, CCR5) [10] Nevertheless, the dark microglia was found in the circumstances. Interestingly, TREM2 and CD11b expression and extensive synaptic fissure margination in association with amyloid deposition. This suggests that several distinct microglial phenotypes exist, including

the following [11].
In recent years, a unique disease-associated microglia phenotype has been identified in neurodegenerative diseases: the 'disease-associated microglia' (DAM) phenotype, also known as the "microglial neurodegenerative" (MGnD) phenotype, containing marker genes for APOE, TREM2, CSF1, CST7, and SPP1 [12].

2.2.2 Microglia Dysfunction

Various internal and environmental cues may lead to a malfunctioning response in microglia during AD. What is more, many biological events which cause free radicals are caused by transition metals. Fenton-type reactions involving iron and copper are known to create reactive oxygen species (ROS), which injure and kill cellular compartments. Their neurotoxic effects stem not only from increased exposure but also from disturbance of homeostasis and subsequent excitotoxicity or oxidative stress compartmentalization. There are two possible explanations for the altered brain metal metabolism: non-genetic and inherited. It may also show up at levels of intake and release, storage, intracellular metabolism, and control. These investigations have illuminated a number of altered metal-related circuits that result in brain dysfunction. Specifically, they disrupt brain architecture, alter the redox status of the cellular environment, and physiologically stimulate redox reactions [13]. Zinc and iron concentrations in AD patients' senile plaques significantly increase, and the use of metal chelators significantly slows the buildup of Aβ [14]. Specifically, a number of epidemiological studies have demonstrated a strong correlation between aluminum exposure and neurodegenerative illnesses such as AD, PD, and ALS. The neurological system has been demonstrated to be harmed by acute aluminum exposure, but chronic aluminum exposure over time causes the nervous system to age and develop neurodegeneration [15]. The majority of aluminum's neurotoxic consequences manifest in cognitive impairment. Aluminum damages the mitochondria of nerve cells and induces apoptosis and programmed necrosis, Aβ accumulation, aberrant tau protein phosphorylation, glial activation, and alterations in synaptic plasticity [16].

2.3 Other Hypothesis of the Causation

2.3.1 The Senile Plaques (SP)

Evidence from pathology, genetics, biology, and biomarkers has affirmed the significance of the β-amyloid peptide (Aβ) in the development of AD. The neuropathological diagnostic criteria for AD include amyloid plaques, which are mostly made of aggregated Aβ, and NFTs, which are made of microtubule-associated tau protein. Senile plaques have different morphological forms, such as neurotic plaques, diffuse plaques, plaques with dense cores, and plaques of the classic and compact types. The synthesis of Aβ deposits from transmembrane amyloid precursor protein (APP) is mediated by Proteolytic cleavage enzymes such as beta and gamma secretase. These enzymes cleave APP into segments of 43.45, 46, 48, 49, and 51 amino acids, ultimately yielding Aβ40 and Aβ42 [17]. Aβ monomers exist in a variety of forms, including soluble oligomers, which may spread throughout the brain, and large, amyloid fibrils that can accumulate into amyloid plaques. Because Aβ plays a significant role in neurotoxicity and neuronal function, the buildup of thicker plaques in the cerebral cortex, hippocampus, and amygdala can result in cognitive deficits as well as astrocyte and microglial activation, axonal and dendritic damage, and synapse loss [5].

2.3.2 NFTs

NFTs are pathological threads of hyperphosphorylated tau protein that can coil around each other at certain stages to form paired helical filaments (PHFs). These filaments accumulate, resulting in loss of tubulin-associated proteins and cytoskeletal microtubules, in the cytoplasm of neuronal perikaryal axons, dendrites, and neuronal perikaryal cytoplasm [5].

3. Risk Factors of AD

3.1 Aging

Aging has the largest effect about the development of AD. It is rare for younger people to get the disease, and most cases of Alzheimer's begin later in life, usually around the age of 65 [17-19]. Affecting multiple organs and cell systems, the aging process is complex and unalterable. ventricular swelling in certain areas, with subsequent deposits in NFTs and SPs. In addition, as people age, a number of conditions can manifest themselves. These include depression, mitochondrial dysfunction, glucose hypometabolism, cholesterol dyshomeostasis and cognitive decline. It might be challenging to differentiate between cases of early AD since normal aging also causes these changes.. Based on age of onset, AD may be classified into two groups: early-onset AD (EOAD), which is an uncommon variety with only 1-6% of cases; most instances in this group are familial AD, this is defined as multiple individuals in multiple generations with Alzheimer's disease, and may range in age from 30 to 60 or 65. The second type is called late-onset AD (LOAD), and it is more prevalent in those whose onset ages are beyond 65. Those with a family history of Alzheimer's disease or a family with a

ISSN 2959-409X

late-onset illness may experience both forms of AD [18].

3.2 Genetic

Genetic factors also play a major role in AD. 70% of the cases of AD were linked to genetic factors: mutations in dominant genes such apolipoprotein E (ApoE), amyloid precursor protein (APP), sesenilin-1 (PSEN-1), sesenilin-2 (PSEN-2), and most instances of EOAD are inherited in an autosomal dominant manner [19].

3.3 Environment Factors

Aging or genetic risk factors do not explain every case of Alzheimer's. Air pollution, diets, metals, infectious diseases, and numerous other environmental risk factors may induce oxidative stress and inflammatory responses that increase Alzheimer's disease susceptibility. The following are some of the most important environmental elements and their links to Alzheimer's disease [20].

3.3.1 Atmospheric pollution

Because of the released chemical, physical, biological pollution, air pollution is an increasingly serious problem. The NAAQSs list six air pollutants—O3, NOx, CO, particulate matter (PM), SO2, and particulate matter—as hazardous to human health. Investigate using both animal and cellular models have demonstrated that exposure to high concentrations of air pollution can cause harm to the bulb and olfactory mucosa in addition to the frontal cortical region, comparable to that seen in Alzheimer's disease. Neurodegeneration oxidative stress, and neuroinflammation are associated with exposure to air toxins and the presence of hyperphosphorylated tau and Aβ plaques in the frontal cortex. Air pollution has been linked to increased development and buildup of Aβ42 as well as decreased cognitive performance [21].

3.3.2 Diet

Studies examining the connection between diet and AD have multiplied in the last several years. High calorie intake and omega-3 fatty acids have been linked to an increased risk of AD, whereas some vitamins, polyphenols, and other dietary supplements, antioxidants, and fish, have been shown to reduce the risk of AD [22]. Processing food causes heat sensitive micronutrients to break down (like vitamin C and folates), significant water loss, and the creation of hazardous byproducts called advanced glycation end products, which are created when enzymes do not glycate free amino groups in lipids, proteins and nucleic acids. Because AGEs modify the structure and function of body proteins and cell surface receptors, they can cause oxidative stress and inflammation, which is known as their toxic effect. Numerous investigations have shown a correlation between the advancement of AD and cognitive loss when serum levels of AGEs are high. Acting as a transporter and as a cell surface receptor for Aβ, RAGE is found in several bodily tissues, including as microglia and astrocytes. It has been shown that it is over-expressed in the brain of AD patients. Poor diet is another risk factor for AD. Lack of nutrients like folate, vitamin D and vitaminB12 can also cause cognitive impairment, as well as diseases associated with eating and eating that cause increased risk of malnutrition [23].

3.3.3 Metal

Metals are naturally occurring and can be found in biological systems. They can be divided into two main categories, as follows: bio-metallic metals, which have physiological functions in living organisms (e.g., Cu, Zn, and Fe), and toxic metals, which have no discernible biological functions (e.g. Al and Pt). Al is a material with a wide range of applications in various industrial sectors, including the processing of foodstuffs, the manufacture of cosmetics, the production of medical products and the synthesis of pharmaceuticals. In the human body, Al binds to citrate and transferrin in plasma, making it easier for aluminum to be transported to brain. Aluminum has been shown to accumulate in the cortex and hippocampus, interact with proteins, resulting in improper folding, aggregation and post-translational modification of highly modified proteins like tau, which are characteristic of AD. [24].

4. Treatment for the Hypothesis of Neuroinflammation

If you follow the "checklist" your paper will conform to the requirements of the publisher and facilitate a problem-free publication process.

4.1 Inhibition of the Stimulation of Microglia

There are many factors, such as aging, stress, age, or systemic inflammation, cause imbalances in the CNS, leading to the formation of microglia and a strong sensitivity and response to inflammatory stimuli. Therefore, inhibiting microglial early growth before disease onset may be a viable therapy method for AD. Studies have shown that patients with obesity and insulin resistance in the middle years of AD are prone to inflammation, whereas statins protect against these injuries, preventing microglia from forming [25]. In addition, the use of vitamin E and omega-3 fatty acid supplements also causes neuroinflammation and reduces inflammation in the brain and blood of AD patients [26].

4.2 The Objective is to Inhibit the Pro-inflammatory Reaction

The factor NF-κB is important in the physiological procedures involved in cognition, memory and signaling in the NSC. This phenomenon can be triggered by neuroinflammation, oxidative stress, resulting in the malfunction of the CNS in patients diagnosed with AD. [27]. ROS production serves to initiate the enzyme activity of IKKb, which in turn phosphorylates the heterodimer of NF-κB. This process results in the inhibition of the kappaB (IB) pathway, which is then degraded by the ubiquitous protein pathway. However, the dissociation of IB from the dimer can initiate the flow of NF-κB into the nucleus. [28]. Activating NF-κB suggests that BACE1 expression and Aβ processing stimulate and may be a new molecular mechanism that regulates AD evolution. Polyphenols, antioxidants, and nonsteroidal anti-inflammatory drugs that inhibit NF-κB activation have been shown to reduce the burden of Aβ.

4.3 Microglial Phenotypic Variation Regulation

In the initial phases of Alzheimer's disease, microglia remove toxic damage to support neuronal activity. Interference with microglia's activation may prolong the anti-inflammatory action of these cells. In the setting of AD in mice, the use of PPAR-γ activators, such as pioglitazone and rosiglitazone, microglial induction was observed to adopt an anti-inflammatory phenotype by phagocytosing, while active PPAR-γ itself may suppress the inflammatory response. [29].

4.4 Future Prospect

Patient therapy is still difficult due to the intricacy of AD. Memantine and cholinesterase inhibitors, or these two drugs combined, are the only approved treatments for AD at the moment. On top of that, a considerable number of novel pharmaceuticals have been unsuccessful in the larger phase III clinical trials., failing to satisfy efficacy endpoints, despite early promise. The complex aetiologia of AD, the present limitations in our understanding of the links between the different pathways involved in the development of Alzheimer's disease and the ensuing neurodegeneration, and the potential inefficacy of the existing therapeutic modalities are the primary factors contributing to the high attrition rate observed in AD-related clinical trials. Even if the combination of memantine and cholinesterase inhibitors hasn't worked well for treating AD, it's possible that treating several routes will be necessary for effective care. Thus, more experiments examining rational agent combinations ought to be carried out in the future [30].

5. Conclusion

It is undeniable that the AD brain experiences neuroinflammation. It is easy to identify mechanisms that resemble those found in localized peripheral inflammatory responses and to delineate the intricate routes through which these mechanisms interact. The continuous existence of very insoluble deposits of aberrant proteins and chronic tissue damage are two more clear similarities between the AD brain and the circumstances that cause localized peripheral inflammation. The fact that AD inflammation wasn't noticed sooner is quite unexpected. The question at hand is what these numerous discoveries actually entail for patients who have AD or may develop it. Overall, AD neuroinflammation is probably responsible for aggravating AD development. Therefore, whatever the final cause of AD may be, medicines that reduce AD neuroinflammation are recommended as a supplementary measure to therapies that target the disease's etiology more specifically. Anti-inflammatory medications won't treat AD any more than NSAIDs will cure arthritis. Anti-inflammatory therapy, however, ought to provide substantial benefits for AD patients provided AD neuroinflammation is addressed with reasonable expectations and thoughtful medication design.

References

[1] Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat Neurosci (2015) 18(6):794–9.

[2] Lecca D, Jung YJ, Scerba MT, Hwang I, Kim YK, Kim S, Modrow S, Tweedie D, Hsueh SC, Liu D, Luo W, Glotfelty E, Li Y, Wang JY, Luo Y, Hoffer BJ, Kim DS, McDevitt RA, Greig NH. Role of chronic neuroinflammation in neuroplasticity and cognitive function: A hypothesis. Alzheimers Dement. 2022 Nov;18(11):2327-2340.

[3] Wang C, Zong S, Cui X, Wang X, Wu S, Wang L, Liu Y, Lu Z. The effects of microglia-associated neuroinflammation on Alzheimer's disease. Front Immunol. 2023 Feb 22;14:1117172.

[4] Conti Filho CE, Loss LB, Marcolongo-Pereira C, Rossoni Junior JV, Barcelos RM, Chiarelli-Neto O, da Silva BS, Passamani Ambrosio R, Castro FCAQ, Teixeira SF, Mezzomo NJ. Advances in Alzheimer's disease's pharmacological treatment. Front Pharmacol. 2023 Jan 26;14:1101452.

[5] Stancu IC, Cremers N, Vanrusselt H, Couturier J, Vanoosthuyse A, Kessels S, et al.. Aggregated tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded tau pathology in vivo. Acta Neuropathol (2019) 137(4):599–617.

[6] Leuti A, Fazio D, Fava M, Piccoli A, Oddi S, Maccarrone M. Bioactive lipids, inflammation and chronic diseases. Adv Drug Delivery Rev(2020) 159:133–69.

ISSN 2959-409X

[7] Ueno M, Fujita Y, Tanaka T, Nakamura Y, Kikuta J, Ishii M, et al.. Layer V cortical neurons require microglial support for survival during postnatal development. Nat Neurosci (2013) 16(5):543–51.

[8] Salter M.W., Stevens B. Microglia emerge as central players in brain disease. Nat. Med. 2017;23:1018–1027.

[9] Kamphuis W., Kooijman L., Schetters S., Orre M., Hol E.M. Transcriptional profiling of CD11c-positive microglia accumulating around amyloid plaques in a mouse model for Alzheimer's disease. Biochim. Biophys. Acta. 2016;1862:1847–1860.

[10] Sarlus H., Heneka M.T. Microglia in Alzheimer's disease. J. Clin. Investig. 2017;127:3240–3249.

[11] Qin Q., Teng Z., Liu C., Li Q., Yin Y., Tang Y. TREM2, microglia, and Alzheimer's disease. Mech. Ageing Dev. 2021;195:111438.

[12] Lovell M.A. A Potential Role for Alterations of Zinc and Zinc Transport Proteins in the Progression of Alzheimer's Disease. J. Alzheimer's Dis. 2009;16:471–483.

[13] Cherny R.A., Atwood C.S., Xilinas M.E., Gray D.N., Jones W.D., McLean C.A., Barnham K.J., Volitakis I., Fraser F.W., Kim Y., et al. Treatment with a copper–zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron. 2001;30:665–676.

[14] Maya S., Prakash T., Madhu K.D., Goli D. Multifaceted effects of aluminium in neurodegenerative diseases: A review. Biomed. Pharmacother. 2016;83:746–754.

[15] Sharma D.R., Wani W.Y., Sunkaria A., Kandimalla R.J., Sharma R.K., Verma D., Bal A., Gill K.D. Quercetin attenuates neuronal death against aluminum-induced neurodegeneration in the rat hippocampus. Neuroscience. 2016;324:163–176.

[16] Chen G.F., Xu T.H., Yan Y., Zhou Y.R., Jiang Y., Melcher K., Xu H.E. Amyloid beta: Structure, biology and structure-based therapeutic development. Acta Pharmacol. Sin. 2017;38:1205–1235.

[17]]Guerreiro R., Bras J. The age factor in Alzheimer's disease. Genome Med. 2015;7:106.

[18] Bekris L.M., Yu C.E., Bird T.D., Tsuang D.W. Genetics of Alzheimer disease. J. Geriatr. Psychiatry Neurol. 2010;23:213–227.

[19] Cauwenberghe C., Van Broeckhoven C., Sleegers K. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. Genet. Med. Off. J. Am. Coll. Med Genet. 2016;18:421–430.

[20] Wainaina M.N., Chen Z., Zhong C. Environmental factors in the development and progression of late-onset Alzheimer's disease. Neurosci. Bull. 2014;30:253–270.

[21] Moulton P.V., Yang W. Air pollution, oxidative stress, and Alzheimer's disease. J. Environ. Public Health. 2012;2012:472751. .

[22] Hu N., Yu J.T., Tan L., Wang Y.L., Sun L., Tan L. Nutrition and the risk of Alzheimer's disease. Biomed. Res. Int. 2013;2013:524820.

[23] Koyama A., Hashimoto M., Tanaka H., Fujise N., Matsushita M., Miyagawa Y., Hatada Y., Fukuhara R., Hasegawa N., Todani S., et al. Malnutrition in Alzheimer's disease, dementia with lewy bodies, and frontotemporal lobar degeneration: Comparison using serum albumin, total protein, and hemoglobin level. PLoS ONE. 2016;11

[24] Colomina M.T., Peris-Sampedro F. Aluminum and Alzheimer's disease. Adv. Neurobiol. 2017;18:183–197.

[25] Dias HK, Brown CL, Polidori MC, Lip GY, Griffiths HR. LDL-lipids from patients with hypercholesterolaemia and alzheimer's disease are inflammatory to microvascular endothelial cells: mitigation by statin intervention. Clin Sci (Lond).(2015) 129(12):1195–206.

[26] Chen H, Liu S, Ji L, Wu T, Ji Y, Zhou Y, et al.. Folic acid supplementation mitigates alzheimer's disease by reducing inflammation: A randomized controlled trial. Mediators Inflamm(2016) 2016:5912146.

[27] Kounatidis I, Ligoxygakis P. Drosophila as a model system to unravel the layers of innate immunity to infection. Open Biol (2012) 2(5):120075.

[28] Jones SV, Kounatidis I. Nuclear factor-kappa b and Alzheimer disease, unifying genetic and environmental risk factors from cell to humans. Front Immunol (2017) 8:1805.

[29] MEsmaeili MA, Yadav S, Gupta RK, Waggoner GR, Deloach A, Calingasan NY, et al.. Preferential PPAR-alpha activation reduces neuroinflammation, and blocks neurodegeneration in vivo. Hum Mol Genet (2016) 25(2):317–27.

[30] Cummings JL, Tong G, Ballard C. Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. J Alzheimers Dis. 2019;67(3):779-794.