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Review

Neuroinflammatory Mechanisms in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder with an unknown origin, making it difficult to diagnose and treat. The pathological features of AD include extensive loss of neurons, amyloid plaques, and neurofibrillary tangles, among others. Amyloid-beta has been extensively researched, and treatment has been attempted, but with little success in clinical practice. Recently, neuroinflammation has been targeted as a treatment for this disease's progression. The neuroinflammation found in AD patients' brains is associated with several mechanical processes, including cyclooxygenase pathways, cytokines, the complement system, chemokines, and oxidative stress. Oligodendrocytes, microglia, and astrocytes work together among other cells to protect the brain from damage. The review focuses on the neuroinflammatory mechanisms that occur in AD.

Keywords: Alzheimer's disease, amyloid-beta, brain, cytokines, inflammation, neuroinflammation

According to epidemiologic studies, anti-inflammatory medications should be used to reduce the incidence of AD. Yet, these drugs' clinical trials have been unsuccessful.[1] Despite the long-standing research, the etiology of AD remains unclear.[2] Alzheimer's disease is a fatal and progressive neurodegenerative disorder and one of the most common causes of dementia worldwide. Recent findings in AD research suggest that the mechanism of inflammation as a consequence of neurodegeneration should be evaluated in favor of glial activity's role in altering synaptic function.[3-5] The clearance of improperly folded proteins can be impaired by inflammation.[6] There is evidence that inflammatory processes play a role in the pathogenesis of AD.[7] Neuroinflammation has been targeted as a treatment for the progression of AD.

Among things associated with neuroinflammation in the AD brain; are chemokines and cytokines, oxidative stress, mechanistic pathways including cyclooxygenase, and the complement system. Moreover, numerous cells including oligodendrocytes, microglia, and astrocytes, protect the brain from injury.[8] According to animal and human studies, systemic inflammation that occurs outside of the central nervous system (CNS) may be a major factor in causing neurodegeneration, cognitive decline, and AD pathology in older people. In addition, studies on the Neuropathologic and biochemicals of AD patients' brains provide evidence for the involvement of inflammatory pathways.[9] As a result of improper cleavage of the amyloid precursor protein (APP), amyloid-beta (Aβ) monomers assemble to form oligomeric Aβ, and in turn, Aβ fibrils and plaques aggregate.[6] Additionally, a lot of neuron loss is observed.[10] While genetic research has provided strong support for the etiologic involvement of immune function in AD, findings from translational and epidemiologic studies indicate that systemic inflammation (inflammation outside the CNS) may confirm Alzheimer's-specific pathology in the brain. According to studies, individuals with mild cognitive impairment and AD are more likely to have higher levels of inflammatory markers, cytokine receptors, and pro-inflammatory cytokines.[11] These results have led many to question whether systemic inflammation plays a compensatory mechanistic function. Findings

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from significant prospective cohort studies have started seeking answers to this question. According to a recent study, middle-aged people with higher levels of inflammatory proteins in their blood were more likely to experience cognitive loss. Similarly, increased inflammatory protein levels in middle age have been linked to reduced brain volume and abnormal white matter in later age.[12] These data offer crucial new understandings of the temporal link between adverse neurocognitive outcomes and inflammation, suggesting that systemic inflammation may contribute to the progression of neurodegenerative and cognitive decline.

One theory is that those with greater levels of systematic inflammation in middle age are more likely to be exposed to the harmful consequences of systematic inflammation, and to endure chronic increases in inflammation, even if midlife inflammation may be a primary predictor of later dementia. To support this hypothesis, a study longitudinally examining inflammatory blood markers discovered that, even when complex factors like comorbidity were taken into account, people who had high levels of inflammatory proteins for many years from their mid-to-late age had relatively worse neurocognitive outcomes.[13] Observational studies demonstrating a decreased incidence of AD later in life in those who regularly take anti-inflammatory medications like ibuprofen supports this theory. According to these observational studies, peripheral inflammation, which develops prior to typical dementia onset, may impact cognitive aging and AD progression.[14]

BRAIN MICROENVIRONMENT

The arachnoid barrier, the blood-cerebrospinal fluid barrier, and the blood-brain barrier are the tight barriers by which the brain defends itself from invading substances. By creating a tightly controlled and evenly managed microenvironment within the CNS, these barriers provide protection against exterior elements like toxins, pathogenic agents, and peripheral pro-inflammatory cytokines.[15] However, brain function is known to be impacted by acute systemic viral or bacterial inflammation. Evidence from both preclinical and clinical investigations shows that systemically induced inflammatory mediators signal to the brain's humoral and neuronal pathways.[16]

Kynurenine Pathways

It is considered that kynurenines-a mechanism that modifies the number of metabolites produced by the breakdown of the essential amino acid tryptophan-favor neurodegenerative disorders and inflammatory conditions. Numerous bioactive intermediate metabolites, such as quinolinic acid, kynurenic acid, 3-hydroxyanthranilic acid (3-HAA), and 3-hydroxykynurenine (3-HK), is produced as a result of this degradation.[17] These metabolites can directly target neurotransmitter receptors, have an impact on reduction-oxidation processes, and control the activity of cells. The ubiquitously expressed indoleamine 2,3-dioxygenases 1 and 2 (IDO1 and IDO2) regulate extrahepatic tryptophan breakdown.[18] Under standard settings, IDO does not have a high activity level. However, their activity is significantly boosted when stimulated, like by pro-inflammatory cytokines in immune cells.[19]

High levels of inflammation are directly linked by interferon-gamma to the production of potentially dangerous kynurenines that can alter brain Physiology. It has been proven that cytokines' non-transient IDO activity results in the overproduction of the cytotoxic and neurotoxic metabolites 3-HAA, 3-HK, and quinolinic acid. Free radicals are produced via the interactions of 3-3-hydroxykynurenine and 3-3-hydroxyanthranilic acid with metals as well as by autooxidation. An N-methyl-D-aspartic acid receptor agonist, quinolinic acid can increase glutamate release and cause excitotoxicity while also producing free radicals.[20] Additionally, the tau protein's phosphorylation, a key player in AD, is increased by quinolinic acid.[21] The brain contains fewer IDO than other regions. But 3-HK and tryptophan can get through the blood-brain barrier, and immune cells' peripheral production of these metabolites contributes significantly to their levels in the brain, where they can be broken down by glial cells and infiltrated into macrophages. The concentration of the harmful paranoid increases in the blood under non-transient activity, thus, leading to local concentrations of glial and neuronal cells rising to hazardous levels in the brain.[20]

Inflammasomes, multiple sclerosis, traumatic brain damage, and AD are some neurological disorders attributed to cytoplasmic multiprotein complexes of the innate immune system. Damage-associated host proteins initiate inflammation through a signaling cascade triggered by inflammasomes and pathogens. Pro-interleukin-18 and pro-interleukin-1 beta are cleaved into mature forms by the enzyme caspase-1, which regulates pro-inflammatory cytokines. This activation occurs in the final cascade of molecular events brought on by inflammation. For instance,

gasdermin D is cleaved by caspase-1, forming membrane pores from the N-terminal fragment and followed by cytokine release and subsequent cell death.[22]

The nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) in microglia may play a role in AD, according to an earlier animal study. In the brains of individuals with mild cognitive impairment or AD, compared to controls in the mouse model, a high concentration of cleavage caspase-1 and APP/presenilin-1 were found.[23] In these mice with genetic AD mutations, genetic deficiency of caspase-1 or NLRP3 reduced Aβ accumulation and protected against memory loss. Inflammation of NLRP3 promotes the development and progression of amyloid precursor pathology in AD-bearing mice. Moreover, studies in Tau22-mice show that NLRP3 is necessary for tau aggregation and hyperphosphorylation. Its expression as an ATPase enzyme suggests that it has therapeutic potential.[24] In a rat model of AD amyloidosis, regenerative therapy with the NLRP3 inflammatory inhibitor MCC950 decreased issues with long-term potentiation.[25] Additionally, in another study of experimental autoimmune encephalomyelitis, dapansutrile, another NLRP3 inhibitor, was shown to provide protection against spinal cord demyelination and functional impairments.[26] Therefore, inhibitors of the brain-permeable NLRP3 or broad inflammation inhibitors are highly relevant as neuroprotectors, regardless of whether infectious pathogens act as stimulants to trigger inflammation.

Alzheimer's disease is categorized as a type of dementia with a high prevalence among older people. Memory loss, confusion, and cognitive impairment are the main symptoms.[27] It is believed that the disease's neuropathological processes, such as inflammation, the buildup of neurofibrillary tangles and amyloid plaques, and neuronal and synaptic loss, accumulate 10-20 years prior to the onset of clinical symptoms.[28] Amyloid-beta plaques and neurofibrillary tangles are the two main pathologies associated with AD. The disease's pathology is brought on by improper cleavage of the APP, which leads to the oligomerization of Aβ monomers to produce Aβ plaques and fibrils. It is believed that APP is involved in cell health and growth.[6]

The production and removal of Aβ monomers, as well as their accumulation in oligomeric Aβ forms, are crucial factors in determining how AD pathogenesis begins. While alpha- and gamma-secretases break down non-amyloidogenic proteins to produce soluble pieces of the APP, Aβ plaques are created in the brain when defective beta and gamma-secretase cleave APP, producing insoluble Aβ peptides.[29-30]

Some risk factors increase the likelihood of developing AD. Traumatic brain injury, cardiovascular alterations, metabolic illnesses including diabetes, and aging are a few of these.[5]

In Alzheimer's disease, hyperphosphorylated tau tangles are found less frequently than Aβ plaques.[31] Neurofibrillary tangles are brought out by tau hyperphosphorylation, a microtubule-associated protein that stabilizes microtubules. While phosphorylation of tau protein removes it from microtubules, allowing transport, dephosphorylation returns tau protein to the microtubule, which is essential in intracellular trafficking. Multiple sites on tau are phosphorylated in AD, which disrupts a number of cellular processes, including the removal of tau protein from microtubules and the microtubule collapse. Neurofibrillary tangles are created when hyperphosphorylated tau builds up as paired helical pieces, and this buildup, in turn, results in neuronal malfunction, subsequent death, and impaired cellular function.[32]

Inflammation is a complex defense mechanism that generally occurs in response to altered homeostasis and agitation.[33] The term "neuroinflammation" broadly refers to inflammatory reactions that take place in the innate CNS and include adaptive immune systems. Brain development is excessively facilitated by these mechanisms. The pathogenic processes implicated in neuronal death in AD are intracellular and extracellular autonomic activities. Furthermore, the gene expression of anti-inflammatory and pro-inflammatory cytokines can be disrupted by defense systems against damage, poisons, and infection brought on by a variety of other causes, which initiates chronic neuroinflammation and stimulates a number of microglial cells and cytokines.[34] If pro-inflammatory and anti-inflammatory signaling goes wrong, as it does in AD, chronic inflammation results. Acute inflammation in the brain is a good defense against injury, infection, and toxins. Additionally, it is related to the protracted release of cytokines and the activation of microglia. It has been suggested that the prolonged inflammatory response seen in AD patients' brains is a reaction to the neuronal loss that characterizes this condition. Significant research has revealed that a persistent immune response in the brain not only contributes to neurodegeneration but also promotes and exacerbates pathologies of Aβ plaque and neurofibrillary tangles.

Numerous studies now suggest that the development of the neuropathologic abnormalities identified in AD is fundamentally involved with neuroinflammation. Reports of immune-related cells and proteins nearby Aβ plaques have been made since 1980. Anti-inflammatory medications used to treat conditions like rheumatoid arthritis provide a defense mechanism against AD, according to observational and epidemiological studies published since 1990.[35] These studies have sparked research using transgenic AD models in animals that suggest non-steroidal anti-inflammatory medications may alleviate AD pathogenesis. The outcomes of human trials involving non-steroidal anti-inflammatory medicines have been inconsistent and lack solid proof.[36] Thus, neuroinflammation, which is expected to worsen the disease in addition to other risk factors and hereditary causes of AD, is not considered a particular cause in and of itself.

Encephalitis appears to have a two-sided function, resampling a neuroprotective agent during the acute phase response, however, when a chronic response occurs, it becomes unfavorable.[37] Numerous hazardous and pro-inflammatory substances, including cytokines, reactive oxygen radicals, and nitric oxide, are released by chronically activated microglia. It has been shown that elevated levels of interleukin-1 are responsible for elevated APP development and Aβ in individuals who have recently died from head trauma. This increase in cerebral Aβ aggregates occurs 1-3 weeks after injury. It has been demonstrated that neuroinflammation in AD significantly contributes to the aggravation of tau hyperphosphorylation and amyloid protein burden.[38]

Microglia

The CNS contains resident immune cells called microglia, which are visually described as little-branched soma cells and are not active in an unaffected brain. Cell processes extend and retract to evaluate their environment before making contact with other glial cells and neurons. Cell somas are stable. Many different signaling pathways are in charge of the surrounding neuronal environment. Numerous chemokine and cytokine receptors, as well as receptors like fractalkine, which binds ligands that are constitutively produced in non-patient neuronal settings, are used to monitor the local neuronal environment. Microglia cells activate when they detect a threat to the CNS, such as disease, damage, or invasion. This morphological shift leads to the retraction of processes and cell expansion and migration.[39]

It is believed that Aβ is the primary factor activating microglia in AD, leading activated microglia cells to respond by migrating to Aβ plaques and engaging in phagocytosis. In animal modeling systems, the immune response has been demonstrated to have favorable impacts on AD-related diseases resulting in the clearance of APP early in AD pathogenesis.[40] Additionally, reactive microgliosis, a term used to describe the sustained activation of microglia cells in a feed-forward cycle, has been proven to contribute to the immune response's long-term ability to exacerbate AD pathology. Neuronal damage is triggered by the buildup of APPs and a persistently dysfunctional pro-inflammatory cytokine. Furthermore, persistent activity reduces the capacity of microglial cells to bind and phagocytize Aβ and the activity of Aβ-degrading enzymes, which impairs the ability to break down Aβ plaques. The data, nevertheless, showed no impact on the ability of microglial cells to produce pro-inflammatory cytokines. It highlights a distinctive aspect of the pathogenesis in that immunological function is preserved, although the total clearance of APP is reduced. Increased microglia activity, which accelerates neurodegeneration and exacerbates neuroinflammation, results from the continuous production of pro-inflammatory cytokines and associated neurotoxins from microglia cells.[39-41]

Microglia cells produce a number of pro-inflammatory cytokines in the plaques since they are engaged in the removal of APPs. According to recent research, peripheral macrophages can be drawn into the APP plaque accumulation to clear them when the ability of microglia cells to remove Aβ plaques weakens. The consequences of inflammation and, subsequently, AD pathogenesis are continuously increased when peripheral macrophages are introduced into the brain. Recent evidence that a mutation in a triggering receptor expressed on myeloid cells-2 (TREM-2) is more likely to develop AD provides some of the most compelling findings on the significance of inflammation in the control of the immune response and the pathogenesis of AD. A small number of missense mutations in myeloid cells result in a significantly increased risk of AD.[42]

Astrocytes

Astrocytes, the most prevalent glial cells in the CNS, play a crucial role in the upkeep and structure of the brain. They work in tandem with neurons to process information and convey signals, control energy metabolism, maintain ionic equilibrium, modulation of oxidative stress, emit neurotransmitters, and

remodel synapses.[43]

In the early stages of AD, active astrocyte cells can be found in the molecular layer of the cerebral cortex and close to the Aβ beneath the pyramidal cell layer.[44] Although the mechanisms triggering the activation of astrocytes in response to the pathogenic alterations brought on by AD are not fully understood, amyloid has been found to activate astrocyte cells. The clearance of Aβ that has been deposited in the parenchyma is considerably aided by the ability of activated astrocyte cells to phagocytize and break down amyloid.[45,46] Localized inflammation brought on by the activation of microglia and astrocyte cells may speed up the death of neurons.[47]

Astrogliosis, characterized by an increase in the motility, size, and quantity of astrocyte cells, is a process in which the inflammatory response in AD patients manifests itself as changes in microglial morphology. Numerous neurodegenerative disorders include astrocyte cell activity, characterized by highly expressed glial fibrillary acidic protein, nestin, and vimentin. As a result of these changes, astrocyte cells' regular activities-which are necessary for appropriate neural function-are disrupted.[48] For instance, glutamate concentration in the extracellular space must be maintained for normal physiological processes to occur; when the balance is off, local neuronal depolarization results, which causes cytotoxic damage.[49] While astrocytic activity plays a surveillance role in the brain, excessive activity worsens neuronal damage and hastens the progression of the illness.

As with microglia, astrocyte cells respond quickly to injury and are close to the fibrillar APP aggregates that cause the astroglial activation observed in AD patients. A variety of receptors, including the advanced glycosylated end product receptor, scavenger receptors, proteoglycans, and receptor-like density lipoproteins, are expressed on the cell surfaces of activated astrocyte cells that bind APP peptides. As a result, stimulated astrocyte cells can promote neurite outgrowth, induce neurodegeneration, and express inflammatory-related molecules such as S100 calcium binding protein, which is correlated with the number of dystrophic neurites in AD patients.[48]

Oligodendrocytes

The envelope axons are created by myelin sheaths and oligodendrocytes, which are critical for neurotransmission. In other neurological disorders, myelin and oligodendrocytes are also immune response targets. Despite the fact that AD research in this area has not progressed significantly, focal demyelination of axons associated with myelin abnormalities and lesions in the AD white matter and Aβ deposits in the gray matter has been shown by electrophysiological, histological, imaging, and molecular data.[50] Amyloid precursor protein stereotaxic injection causes myelin degradation, oligodendrocyte loss, and microglial proliferation to rise in the corpus callosum.[51] Furthermore, oligodendroglia have a low glutathione concentration and a high iron content, making them particularly susceptible to oxidative stress.[52] It has been demonstrated that oligodendrocytes express messenger ribonucleic acids (mRNAs) and are immunoreactive to complement components. When membrane cofactor protein is expressed by cells and low amounts of complement component 1 inhibitor (C1INH), complement activity is generated in oligodendrocytes by complement component 1q (gC1qR) binding to myelin oligodendrocyte glycoprotein.[53]

Neurons

In order to defend themselves from inflammatory attacks, neurons are composed of a variety of chemicals. Surface differentiation antigen-22, surface differentiation antigen-200, chemokine ligand-1, trigger receptor-2 expressed on myeloid cells, and surface differentiation antigen-59, a complementary defensive protein, are some of these molecules. It has been discovered that AD renders several of these defense mechanisms ineffective. In the brains of AD patients, surface differentiation antigens 200 and 59 are explicitly diminished in pathologically vulnerable regions.[54,55]

In conclusion, microglia are grouped around neuritic plaques in the AD brain. Advances in imaging analysis, cumulative scientific information, and diagnostic tools-while not entirely clear at the preclinical stage-have strengthened our understanding of the clinical development of the illness and contributed to the molecular complexity of AD. The aspects mentioned in this review, including peripheral elements, protective cells and systems, mitochondrial damage, and tau phosphorylation, among many other essential elements, point to the involvement of the inflammatory cascade and Aβ oligomers as early steps in the pathogenic scenario of AD. Control of amyloid deposits and inflammation is not a new objective in the treatment of AD; many studies have been launched to test the effect of anti-inflammatory or anti-amyloid drugs, but so far, no conclusions have been obtained. Investigations can be improved in three main ways: by using particular

tools but also by developing a multifactorial strategy compatible with the various AD-related changes; by identifying the suitable inflammatory markers that, in combination with genotype information, can individually tailor treatment in accordance with the principles of precision medicine; and by optimizing the timing and schedule of treatment at a preclinical stage. While some of these objectives are relatively easy to achieve in principle, others call for a significant investigation to find viable solutions. To design novel studies where the quality of the chosen patients is prioritized, close cooperation between all experts at all levels is essential.

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