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Neuroinflammation in Alzheimer's Disease: Pleiotropic Roles for Cytokines and Neuronal Pentraxins

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Abstract

Neuroinflammation is a potential factor speculated to underlie Alzheimer's disease (AD) etiopathogenesis and progression. The overwhelming focus in this area of research to date has been on the chronic upregulation of pro-inflammatory cytokines to understand how neuroinflammatory mechanisms contribute to neurodegeneration. Yet, it is important to understand the pleiotropic roles of these cytokines in modulating neuroinflammation in which they cannot be labeled as a strictly "good" or "bad" biomarker phenotype. As such, biomarkers with more precise functions are needed to better understand how neuroinflammation impacts the brain in AD. Neuronal pentraxins are a concentration- dependent group of pro- or anti- inflammatory cytokines. There is contradictory evidence of these pentraxins as being both neuroprotective and potentially detrimental in AD. Potential neuroprotective examples include their ability to predict AD-related outcomes such as cognition, memory function and synaptic refinement. This review will briefly outline the basis of AD and subsequently summarize findings for neuropathological mechanisms of neuroinflammation, roles for traditional pro-and anti-inflammatory cytokines, and data found thus far on the neuronal pentraxins.

Keywords

Alzheimer's disease; inflammation; immunology; memory; pentraxins; biomarkers

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1. Introduction

Alzheimer's disease (AD) is clinically characterized by global cognitive impairment, memory decline, loss of activities of daily living, a neural accumulation of tau and amyloid, and neuronal death manifesting as profound atrophy in important brain regions. There is a current rise in AD prevalence, with research projecting that by the year 2050 one new case of AD will develop every 33 seconds and nearly 1 million new people will develop it annually in the United States [1]. The first signs of atrophy appear in the hippocampus and medial parietal lobe, with subsequent degeneration in the inferolateral region of the temporal lobe and the frontal lobe [2]. Currently, it is thought that Aβ plaques, and tau-based neurofibrillary tangles (NFT) are the main progenitors of the disease and thus are pathogenic hallmarks used for clinical diagnosis post-mortem [3–5]. This classification relies on a method that takes into account the age of the individual with the number of plaques and tangles that are present [4]. However, new proteomics research has suggested a different paradigm to better understand the multitude of factors that mechanistically contribute to the etiopathogenesis and progression of AD, which may complement or act downstream of amyloid and tau pathology [6–9].

AD is typified by progressive medial temporal lobe (MTL) atrophy and memory decline [10,11]. Some proposed mechanisms that trigger these etiopathogenic effects include but are not limited to oxidative stress [12], insulin resistance [13–17], and mitochondrial degradation [18–25] which cause cell damage via release of reactive nitrogen and oxygen species (RNS, ROS) [26,27]. In 2015, the emergence of neuroinflammation as a potential contributing factor for the cause of AD prompted the Alzheimer's Association Roundtable to meet and analyze its mechanistic contributions to the disease [28]. They concluded that there is a very present need for scientific research to advance the understanding of the molecular patterns of neuroinflammation that underlie the various stages of AD, and to find novel biomarkers of inflammation and innate immunity that could be used in the therapeutic prevention and treatment of AD [29–35].

2. Neuroinflammation

Chronic neuroinflammation can induce cellular damage through inflammatory cell proliferation, ROS production, and extensive DNA alterations [36–38]. Physiologically, the process of neuroinflammation is most commonly initiated in response to some sort of a cue such as infection [39], brain injury [40], stress [41], or aging [42], prompting microglia to become activated [43].

Neuroinflammation has consistently been associated with both normal brain aging and AD neurodegeneration [44,45]. Chronic neuroinflammation can begin to degrade tissue and the Blood Brain Barrier (BBB), causing activated microglia to release proinflammatory cytokines to act on peripheral immune cells, generating an immunological response through inflammatory modulation [46]. Chronic neuroinflammation causes a sustained cytokine release, which can ultimately compromise brain tissue through inflammatory, atrophic effects on brain volume [47]. This process leads to neurodegeneration and cognitive deficits [48,49], which are known to be associated with AD [10,11,50].

Traditionally, most research has focused on the role of neuroinflammatory mechanisms that potentiate AD-related pathogenesis [51] and neurodegenerative processes [52–54]. There are two main areas of thought as to how this neuropathologic inflammatory cascade of events occurs: 1) the "inflammation hypothesis" indicates that neuroinflammation is caused by Aβ and tau species [27,55]; or 2) that inflammation-activated microglia cannot properly phagocytose Aβ, leading to plaque accumulation rather than plaque clearance, thereby contributing to Aβ-induced neurodegeneration [56,57]. Yet, it has been proposed that chronic neuroinflammation could precede Aβ and tau pathology in late-onset AD [27,58–60]. Longitudinal brain atrophy in AD is mediated by increased levels of the cardinal pro-inflammatory cytokines, including tumor necrosis factor- α (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6) [56], as well as their downstream effectors (Griffin et al., 1989). The majority of these cytokines are released from microglia, as well as astrocytes, brain endothelial cells (BECs), and neurons [51,56,62,63]. Regardless of how neuroinflammation and both Aβ and tau tie together, there is an overwhelming consensus on their adverse impacts. It has been firmly established that increased levels of neuroinflammation are mechanistically detrimental and can potentiate hippocampal atrophy and memory decline over time [27,64,65]. Furthermore, microglia are thought to play opposing roles in this process, in that they can clear Aβ yet also continually release pro-inflammatory cytokines based on their pleiotropic nature [66]. Next, it is worthwhile to expand on what roles microglia play in acute and chronic neuroinflammation [67].

3. Microglia and Neuroinflammation: Beneficial and Detrimental Roles

Microglial activation in AD is most often thought to be potentiated by Aβ peptides, tau, and neuronal cell degradation [67–71]. Microglia also have prominent roles in the homeostatic regulation of synaptic plasticity and neuronal pathways [72–75], including the activation of the nuclear factor-kappa B (NF-kB) pathway in neurodegenerative disorders [76]. This is important as many chronic diseases are found to be associated with the dysregulation of the NF-kB cellular response pathway due to its explicit functions in gene expression, immunity, modulation of inflammation and disease progression [77]. Microglia also act as an important component of the healthy central nervous system (CNS), when they are unchallenged, through their role in neurogenesis [78].

Yet, microglial cells are a "double-edged sword" based on their level of activation. For example, neurodegenerative disorders are related to microglia retracting and instigating phagocytosis, causing them to no longer maintain homeostatic regulation of synaptic processes [35,79,80]. Microglial cells show phenotypic alterations and become "primed" in the presence of pro-inflammatory cytokines, morphing from a M2c repair oriented phenotype to an active M1 phenotype [81]. This shift identifies a change in the microglia from a protective state of repairing tissue and resolving inflammation to a pro-inflammatory state [82]. In a study that looked at young and aging transgenic mice, it was concluded that in contrast to a healthy, young brain, the aging brain is found to have elevated levels of activated microglia that are associated with an increased expression of classic pro- and anti-inflammatory cytokines biomarkers such as TNFα, IL-1β, IL-6, and IL-10 [83].

Microglial activation also induces expression of inflammatory genes, accounting for the pervasive upregulation of pro-inflammatory cytokines and enzymes as well as pro-inflammatory adhesion molecules of the immune system [84]. It has been corroborated that microglia can be primed toward a pro-inflammatory state by the C3 receptor [85]. An *in vivo* study that continually induced a microglial inflammatory phenotype in mice, using lipopolysaccharide (LPS), showed an activation of the microglial complement-phagosome pathway that subsequently induced neurodegeneration [86].

Evidence continues to confirm that in the aged and neurodegenerative brain, there is a primed microglial state that elicits an "aggressive phenotype" in response to the inflammatory changes that occur in the microglial environment, resulting in a local production of pro-inflammatory cytokines [87]. Experimental in *vivo* results have shown that it is the microglia that links the periphery to the brain and stimulates inflammation in the CNS, which is similar to the inflammatory responses evoked in aging and AD [88]. In this novel experiment, LPS treatments induced systemic inflammation and upregulated the expression of pro-inflammatory cytokines including pentraxin 3. This resulted in increased neuronal death in ME7 mice and an inflammatory cascade of events thought to potentiate neurodegeneration [88].

Since many molecules of the immune system can demonstrate pleiotropic functions, characterizing neuroinflammatory proteins as a pro- or anti-inflammatory species provides little information on the actual role of brain inflammation in AD pathology [27,89,90]. While classic pro-inflammatory cytokines such as IL-1β and IL-6 can potentiate brain atrophy, they are not necessarily ideal AD biomarkers due to their pleiotropic nature. For example, pro-inflammatory cytokines at lower concentrations induce and maintain hippocampal long term potentiation (LTP), neural plasticity, brain homeostasis, plaque clearance via activated microglia, and tissue repair (Ben Menachem-Zidon et al., 2011; Goshen and Yirmiya, 2009; Griffin et al., 1989; Mrak and Griffin, 2005), where at higher concentrations these effects are diminished [59,93–99]. Therefore, the expression of pro-inflammatory cytokines by microglia in the brain cannot necessarily be classified as a "bad" phenotype [100–102] as these cytokines elicit multiple effects, based upon concentration, with considerable differences in levels in individuals [103].

Furthermore, the levels at which these cytokines have specific inflammatory effects are context-dependent, and vary from person to person, indicating their multifunctional modulation of the innate immune system [103,104]. Recent research has suggested that a more effective treatment in neurodegenerative pathology would be to re-balance inflammatory signals to limit AD progression [62,102,105]. These paradigms highlight the difficulty in finding effective biomarkers to detect and track AD development and progression. When analyzing the potential use of immunological biomarkers, it is important to understand their mechanistic roles in order to fully grasp their underlying neurophysiology and subsequent effects on the brain.

4. Neurodegenerative Pathology and Neuroinflammation

Neurodegenerative processes that contribute to atrophy and memory decline occur in specific brain areas like the neocortex and limbic system and are characterized by synaptic damage and neuronal death, with these changes corresponding to the classical cognitive impairment and memory loss associated with AD [9,106–110]. In experiments looking at multiple sclerosis (MS), an inflammatory disease characterized by extensive demyelination, it has been found that neuroinflammation has detrimental effects on synaptic transmission, particularly in the hippocampus, further elucidating the hippocampal cognitive deficits and attenuation of synaptic plasticity that result in pathologies due to CNS inflammation [111,112]. AD neurodegeneration has also been found to result in decreased synaptic plasticity and neurogenesis, which reveals that the etiopathogenesis of AD on the brain could affect two neurophysiological factors: a degradation of mature neurons and a decreased generation of new, functional neurons [110,113–116].

It has also been concluded that aging is a crucial factor in the development and progression of AD, leading to inhibitory regulation of synaptic genes in the biological pathways of AD including inflammation, oxidative stress, energy homeostasis and synapse transmission [117–120]. Both pathological cognitive disorders and age-related cognitive decline seem to be similarly related to levels of synaptic plasticity that decrease over time, with the same neurobiological mechanism that occurs in AD paralleling what happens in normal aging, just to a greater extent [121,122]. Gene expression microarrays have revealed that the mechanism of normal aging is associated with inflammation, mitochondrial dysfunction, oxidative stress and altered protein processing, causing effects on neuronal activity and growth and leading to an inflammatory cascade of events in which impairments to neurons and glial function ultimately result in decreased cognition and memory [123].

Changes in synaptic strength are attributed mostly to astrocytes, as they regulate synaptic plasticity and transmission through the release of gliotransmitters and the expression of transporters/receptors on their extracellular surface, which alters neuronal physiology [124–127]. Microglia can act as “sensors” that shift among activation states due to physiological alterations in the brain environment and thus elicit specific effects on synapses and synaptic transmission [128]. One study found that stimulating pro-inflammatory cytokines in aged rats resulted in decreased LTP, where there was an inverse association of increased IL-1β concentration and decreased LTP [129]. Therefore, there is a current need to elucidate prominent cytokines with mechanistic roles in neuroinflammation and the underlying neurodegenerative processes of AD, such as pentraxins.

5. Pentraxins

The pentraxin family is a unique and highly conserved group of acute, immunological proteins known for their “pentraxin signature,” a specific sequence of eight amino acids found within a pentraxin domain that is characterized by a carboxy-terminal made up of roughly 200 amino acids [130]. They are divided into two biochemical classes: short pentraxins and long pentraxins, the latter of which have a long N terminal domain [131–

133]. Pentraxins are a group of humoral pattern recognition receptors that specifically modulate innate, humoral immunity [134].

The long-form pentraxins (NP1, NPTX2, PTX3) and the pentraxin receptor (NPR) have been proposed to function similar to acute phase proteins in response to inflammatory stimuli by activating the complement system and binding and clearing extracellular pathogens, synaptic debris and toxins from the neurons which further elucidates their role of protection and modulation of synaptic plasticity [113,114,134]. Pentraxins have the ability to recognize damaged cells and instigate apoptosis to clear away cellular debris [135–139]. Neuronal pentraxins have been implicated to play an early role in the postnatal brain by refining synaptic sites, yet in NP knockout (KO) mice it has been concluded that there is no effect on hippocampal LTP and long term depression (LTD) [140]. New research has illustrated the pentraxins ability to play a role in regulating the immune system through complement pathway activation and neutralization, as well as their role in regulating inflammatory pathways through complement modulation and clearance of cellular debris by apoptosis [131,139,141,142].

It is also known that neuronal-activity regulated protein (NARP) has been linked to the pentraxin C-reactive protein (CRP) of the acute phase response due to many similarities in structure and its function as a calcium-dependent lectin [142]. In comparison to the limited amount of research that has been done on NARP and pentraxins in general, the function of CRP is well known in the field of immunology and inflammation. CRP, a pro-inflammatory regulatory protein and a known activator of the complement C system in the acute phase response of immunity [143], is speculated to have a mechanistically protective role as it is able to modulate and balance inflammatory reactions via activation or deactivation of the complement system [144]. CRP, notably the first pattern-recognition molecule (PRM) to be discovered, is an immunological pentraxin of humoral innate immunity that can lead to an activation of adaptive immunity and tissue repair [131,139,145]. There are pentraxins that act as a novel immediate-early gene (IEG) which may play a role in neuronal synaptic plasticity and LTP [142,146,147]. It has also been established that synaptic plasticity in MTL is partly regulated by the pentraxin superfamily, such as NPTX2 [148].

It is important to keep in mind that not all pro-inflammatory modulatory mechanisms induce chronic neuroinflammation. *Nptx2b*, the gene for NPTX2 in zebra fish, is able to modulate synaptic plasticity in hyporcretin/orexin (HCRT) neurons through circadian regulatory mechanisms [149], which are affected by both circadian clock balance and sleep deprivation. The concentration of NARP, the protein in rats homologous to NPTX2, is increased in the adult cortex and hippocampus of the brain with beneficial roles in neuronal growth, synaptic physiology and the associated LTP that arises from N-methyl-D-aspartate (NMDA) receptor activation [142]. Xu et al. concluded that NARP, as well as other associated pentraxins like NP1, interact and correspond to synaptic plasticity in the brain through associations with AMPA type glutamate receptors, from development through adulthood [150].

Messenger RNA expression of NPTX2 has also been found to be upregulated in neurons and glia of the substantia nigra and frontal cortex in Parkinson’s Disease (PD), another

neurodegenerative disorder, and is thought to play roles in PD dysfunction as a result of synaptic alterations in the cerebral cortex [151].

Pentraxins, in general, have physiological regulatory effects on the immune system, synapses, inflammation, homeostasis, and apoptosis [131,139,141,142,152,153]. NPTX2 is a novel pentraxin to utilize due to its pro-inflammatory biomarker potential. NPTX2 is a promising IEG that acts in the acute phase of immunity to aid in clearance of extracellular debris (Dodds et al., 1997), a known protective mechanism against neurodegeneration that allows for increased synaptic plasticity potential [148] and by extension, memory [147,155–157]. New research corroborates this with findings concluding that NPTX2 predicts up to 56% of variance in memory decline over 2 years across the Alzheimer's disease spectrum [158]. This novel study analyzed a cohort of 285 subjects, including those that were cognitively normal, mild cognitively impaired or had AD, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and found that higher baseline cerebrospinal fluid (CSF) levels of NPTX2, a known marker of glutamatergic synaptic plasticity, corresponded to less brain atrophy and less memory decline over a two year span [159–161], suggesting that NPTX2 may have some neuroprotective effects.

Additional evidence has also suggested that NPTX2 has strong potential to predict progression of MCI to AD because this biological protein is a marker in CSF of both neuronal degradation and synaptic loss [159,162]. Furthermore, there is exciting new research to corroborate these findings regarding cognitive deterioration in AD including novel significant findings of the association between NPTX2 and AD neuropathological outcomes. A study that assayed NPTX2 levels with a western blot found that levels of this protein were downregulated in all cortical regions that are typically impacted in AD [163]. Another interesting finding in this study was that NPTX2 was able to predict GluA4, the AMPA type glutamate receptor indicative of neuronal circuitry, expression in both aged and AD subjects [163]. Results revealed that in normal aging there is a downregulation of NPTX2 expression that corresponds to decreased GluA4 expression, while in AD, GluA4 becomes more extensively reduced due to simultaneous pathological amyloidosis effects on NPTX2 potentially leading to a greater decline in cognition as seen in neurodegenerative disorders like AD.

7. Discussion

More research needs to be conducted to determine how to prevent or treat cognitive impairment by repairing synaptic plasticity alterations that occur with age-related/AD-related cognitive decline [164]. The pentraxins, specifically NPTX2, may be good biomarkers and mechanistic targets regarding AD neuropathology and their effects on synaptic plasticity [132,165–168]. Through our recent work looking at peptides of NPTX2 as biomarkers [158], we find that peptidomics and other multiplex techniques may reveal novel immunological biomarkers of chronic neuroinflammation or other processes that best predict classical AD neurodegenerative pathologies.

Additionally, it is crucial to focus on the pleiotropic and concentration-dependent roles of neuroinflammatory cytokines in both in normal aging and neurodegenerative populations.

These regulatory proteins cannot simply be labeled as a “good” or “bad” phenotype. These paradigms should be taken into account when selecting a mechanistic approach to detect and track AD pathogenesis. We propose that biomarkers with more circumscribed functions, such as neuronal pentraxins, are needed to better understand how neuroinflammation contributes to cognitive dysfunction and neurodegeneration, specifically in AD.

8. Conclusions

There is a current need of a disease-modifying therapy for AD [169–173]. Furthermore, due to the multifaceted etiopathology of AD, new proteomics research is needed to advance the understanding and diagnostic tools of this disease by looking at the molecular and neurophysiological mechanisms underlying AD [9,174–176]. Analysis of biochemical markers that can be used to diagnose the various stages of this disease, as well as elucidation of neurobiological changes that occur throughout AD, are vital to advancing this field.

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Table A.1

Summary of Biomarkers Under Investigation

Biomolecule/Biomarker	Proposed Mechanism/Rationale
Pentraxins	
Neuronal pentraxin 1 (NP1) **Neuronal pentraxin receptor (NPR)** **Pentraxin 3 (PTX3)**	NP1, PTX3, and NPR function similarly to acute phase proteins in response to inflammatory stimuli by activating the complement system and clearing extracellular pathogens, synaptic debris, and toxins from the neurons. This enables them to play a role in protection and modulation of synaptic plasticity [113,114,134]. Upregulated expression is associated with systemic inflammation that increases neuronal death and contributes to neurodegeneration [88].
C-reactive protein (CRP)	CRP acts as an activator of the complement C system allowing it to play a protective role in modulating and balancing inflammatory reactions, repairing tissue, and increasing adaptive immunity [143,144,139,131,145].
Neuronal pentraxin 2 (NPTX2)	NPTX2 acts in the acute phase of immunity to aid in clearance of extracellular debris which allows for increased synaptic plasticity potential and memory [154,148,147,157,156,155]. It is able to predict up to 56% of variance in memory decline over 2 years with higher levels corresponding to less brain atrophy and memory decline. NPTX2 may hold some neuroprotective effects and potentially predict progression of MCI to AD [158,159,161,160,162]. Downregulated NPTX2 expression corresponds to extensively reduced GluA4 in AD potentially leading to greater cognitive decline, and NPTX2 may be a good biomarker and mechanistic target regarding AD [177,166–168,132,165].
Cytokines	
Tumor Necrosis factor- α (TNF-α) Interleukin-1β (IL-1β) Interleukin-6 (IL-6) Interleukin-10 (IL-10)	Increased levels of the pro-inflammatory cytokines potentially occur before amyloid and tau, mediate longitudinal brain atrophy in AD, cause cellular potentiation of neuroinflammation, and elevate the levels of activated microglia in the aging brain [61,56,51,62,63,83]. Not necessarily ideal AD biomarkers due to their pleiotropic nature when found in differing concentrations [101,100,102,103]. Lower levels are connected to positive effects [61,91,64,92], **where at higher concentrations these effects are diminished** [95–98,94,59,99,93].
Other Proteins	
Neuronal pentraxin 2b (NPTx2b)	Found in zebrafish; rather than inducing neuroinflammation, this modulates synaptic plasticity in neurons through circadian regulatory mechanisms [149].
Neuronal activity-related pentraxin (NARP)	Protein in rats that is homologous to NPTX2. Increased concentration plays beneficial roles in neuronal growth, synaptic physiology, and LTP [142,150].
Complement Component 3 (C3)	Can prime microglia toward a pro-inflammatory state which induces neurodegeneration [84–86].