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Review

The role of inflammation in Alzheimer's disease

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Abstract

Considerable evidence gained over the past decade has supported the conclusion that neuroinflammation is associated with Alzheimer's disease (AD) pathology. Inflammatory components related to AD neuroinflammation include brain cells such as microglia and astrocytes, the classic and alternate pathways of the complement system, the pentraxin acute-phase proteins, neuronal-type nicotinic acetylcholine receptors (AChRs), peroxisomal proliferators-activated receptors (PPARs), as well as cytokines and chemokines. Both the microglia and astrocytes have been shown to generate beta-amyloid protein (Aβ), one of the main pathologic features of AD. Aβ itself has been shown to act as a pro-inflammatory agent causing the activation of many of the inflammatory components. Further substantiation for the role of neuroinflammation in AD has come from studies that demonstrate patients who took non-steroidal anti-inflammatory drugs had a lower risk of AD than those who did not. These same results have led to increased interest in pursuing anti-inflammatory therapy for AD but with poor results. On the other hand, increasing amount of data suggest that AChRs and PPARs are involved in AD-induced neuroinflammation and in this regard, future therapy may focus on their specific targeting in the AD brain.

Keywords: Alzheimer's disease; Neuroinflammation; Glial cells; Beta-amyloid protein; Senile plaques; Chemokines; Complement system; Cytokines; Interleukin; Tumor necrosis factor; Cyclooxygenase; NSAIDS; Steroids; Pentraxins; Nicotinic acetylcholine receptors

Abbreviations: αBTx, α-bungarotoxin; Aβ, beta-amyloid protein; ACh, acetylcholine; AChBP, acetylcholine-binding protein; AChR, nicotinic acetylcholine receptor; AD, Alzheimer's disease; AICD, amyloid precursor protein intracellular domain; AP, amyloid P; APP, amyloid precursor protein; C/EBP, CCAAT/enhancer-binding protein; CNS, central nervous system; NO, nitric oxide; NOS, nitric oxide synthase; ACT, α1-antichymotrypsin; COX, cyclooxygenase; CRP, C-reactive protein; IDE, insulin-degrading enzyme; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; MAC, membrane attack protein; M-CSF, macrophage colony-stimulating factor; MHC II, major histocompatibility complex type II; MIP, macrophage-inflammatory protein; mRNA, messenger ribonucleic acid; NFTs, neurofibrillary tangles; NSAIDs, nonsteroidal anti-inflammatory drugs; PPARs, peroxisomal proliferators-activated receptors; SPs, senile plaques; TNFα, tumor necrosis factor alpha; TNFβ, tumor necrosis factor beta; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration

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Contents

1. Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disorder that is the most common form of dementia affecting people 65 years and older. The pathologic features of AD are the presence of senile plaques (SPs) and neurofibrillary tangles (NFTs) in the brain. SPs are extracellular beta-amyloid protein (Aβ) deposits derived from amyloid precursor protein (APP) while NFTs are intraneuronal structures composed of tau protein. Clinically AD is characterized by impairment in memory, visuospatial skills, complex cognition, language, emotion and personality. Although the exact cause of AD remains elusive, mounting evidence continues to support the involvement of inflammation in the development of AD (Akiyama et al., 2000a).

Traditionally thought of as an immunologically privileged organ, today the CNS is known to have an endogenous immune system that is coordinated by immunocompetent cells such as the microglia. The inflammation associated with the CNS, neuroinflammation, differs from that found in the periphery. The brain lacks pain fibers, making it difficult to recognize the occurrence of inflammation and the classic signs of inflammation such as rubor (redness), tumor (swelling), calor (heat), and dolor (pain) are typically not seen in the CNS. Also, the CNS differs from other organs in that it contains a blood–brain barrier, a system of tight junctions at the capillaries within the CNS that obstructs the entry of inflammatory cells, pathogens, and some macromolecules into the subarachnoid space. Although not complete, this barrier acts to protect the sensitive, fragile, and post-mitotic neurons from the damages typically associated with inflammation.

2. Cellular components of inflammation

The major players involved in the inflammatory process in AD are thought to be the microglia and the astrocytes and possibly to a less extent the neurons, all of which are cellular components of the brain who have many critical roles in the homeostasis and function of the brain (Akiyama et al., 2000a,b).

2.1. Microglia

The microglia are cells that support and protect the neurons and their functions in the CNS and act as immunocompetent defense cells that orchestrate the endogenous immune response of the CNS. The mi-

croglia are composed mostly of mesodermally derived macrophages (Streit & Kincaid-Colton, 1995) and they are able to express major histocompatibility complex type II (MHC II), pro-inflammatory cytokines, chemokines, reactive oxygen species, and complement proteins (Moore & O'Banion, 2002). Microglia also has phagocytic and scavenger properties and depending on the conditions that activate the microglia they can exercise both neuroprotective and neurotoxic functions in the brain (Streit, Walter, & Pennell, 1999).

The microglia play a central role in the cellular response to pathological lesions, such as Aβ and neuritic plaques (Kalaria, 1999). Aβ can attract and activate microglia leading to clustering of microglia around Aβ deposits sites in the brain. Microglia cultured from both AD brains and non-demented brains showed marked chemotaxis to pre-aggregated Aβ deposits (Rogers & Lue, 2001). Microglia can express scavenger receptors that mediate adhesion of the microglia to Aβ fibril-coated surfaces leading to secretion of reactive oxygen species and cell immobilization (El Khoury et al., 1996). Secretion of reactive oxygen species can lead to further damage of neurons via the free radical oxidative damage pathway. Exposure of microglia to Aβ causes activation of the microglia leading to an increase in cell surface expression of MHC II along with increased secretion of the pro-inflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNFα) as well as the chemokines interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α), and monocyte chemo-attractant protein-1 (Rogers & Lue, 2001). Aβ can cause peripherally circulating macrophages to cross the blood–brain barrier via chemokine recruitment, possible leading to an increased inflammatory burden (Fiala et al., 1998). Another potential mechanism for Aβ activation of microglia is mediated through the receptor for advanced glycation end products and macrophage colony-stimulating factor (M-CSF) (Lue et al., 2001). These receptors can bind Aβ and trigger signals leading to cellular activation. M-CSF itself can induce microglial chemotaxis, proliferation, increased macrophage scavenger receptor expression, and enhanced cell survival (Lue et al., 2001; Tomozawa, Inoue, Takahashi, Adachi, & Satoh, 1996).

The presence of activated microglia surrounding Aβ deposits may point to a phagocytic effort by microglia in an attempt to remove Aβ plaques. Aβ has been shown to induce a phagocytic response in microglia in a dose- and time-dependent manner (Kopek & Carroll, 1998). Along with phagocytosis, Aβ can induce expression of nitric oxide synthase (NOS) in microglia resulting in the loss of selected neuron populations, implying neuronal damage resulting from products released by the activated microglia rather than direct action of the Aβ (Weldon et al., 1998). After ingestion of Aβ by microglia, M-CSF over-expressed by the microglia in the vicinity of Aβ deposits can result in enhanced phagocytosis of opsonized Aβ with improved clearance of the deposits (Mitrasinovic & Murphy, 2003). Microglia in rats have also been shown attempting to clear the amyloid from the CNS following phagocytosis and internalization (Frautschy, Cole, & Baird, 1992). Some of these Aβ laden microglias were found to migrate to vessels and to the ventricles in an attempt to rid the brain of the Aβ, resulting in the deposition of the Aβ on the vessels. This may indicate that the distribution of some of the Aβ deposits typically seen in the brain may not be the initial deposition but rather placed there by microglia. A number of reports suggest that once Aβ is phagocytosed by the microglia, it can remain stored and undegraded for days implying limited effectiveness in degrading Aβ fibrils (Frackowiak et al., 1992). The application of peripherally administered antibodies to Aβ was found to reduce amyloid burden by triggering microglial cells to clear plaques through a receptor-mediated phagocytosis and subsequent peptide degradation (Bard et al., 2000). These antibodies were able to cross the blood–brain barrier and act directly in the brain and may offer a therapeutic approach to the treatment of AD. Research has shown that estrogen is another substance that can enhance microglial phagocytosis of Aβ (Li et al., 2000). Pretreatment of microglia with estrogen caused an enhanced dose- and time-dependent uptake of Aβ by the microglia while pretreatment of microglia with an estrogen antagonist significantly reduced internalization of the Aβ. The stimulation of the microglia by estrogen may shed some light on the benefit of estrogen in the brain but clinical trials of estrogen treatment in postmenopausal women and the prevention of AD have not been conclusive regarding this benefit (Sherwin, 2003). The microglia themselves may be a source of Aβ production in the AD brain where they have been shown to secrete Aβ under the influence of Aβ or

pro-inflammatory stimuli (Bitting, Naidu, Cordell, & Murphy, 1996). The production of Aβ by microglia is still a small part of the total Aβ since the major source of Aβ production comes from neurons.

On the other hand, the microglia may play a role in the degradation of Aβ by the release of insulin-degrading enzyme (IDE). IDE is a protease that can cleave a variety of small proteins, such as insulin and glucagon, and has been shown to degrade Aβ (Chesneau, Vekrellis, Rosner, & Selkoe, 2000; Qiu, Ye, Kholodenko, Seubert, & Selkoe, 1997; Qiu et al., 1998). The same studies showed that the use of IDE inhibitors blocked the degradation of Aβ. IDE missense mutations in diabetes mellitus type 2 resulted in a decrease of both Aβ and insulin leading to increased endogenous secretion of Aβ (Farris et al., 2004). Along with amyloid β-protein, IDE was found to regulate the levels of both APP intracellular domain (AICD), a fragment produced by the γ-secretase processing of APP, and insulin (Farris et al., 2003). The researchers also showed that a deficiency of IDE resulted in a decrease in Aβ degradation, AICD, and insulin (causing hyperinsulinemia and glucose intolerance). Another study provided further evidence that IDE is involved in the degradation of AICD and that over-expression of IDE resulted in improved AICD degradation while IDE depletion or inhibition resulted in decreased AICD degradation (Edbauer, Willem, Lammich, Steiner, & Haass, 2002). This further suggests that IDE deficiency or hypofunction may play a role in the disease processes of both AD and diabetes mellitus.

Even at the genomic level, expression of transcription factors related to and involved with inflammation in AD has been shown to be involved in the AD brain. The expression by microglia of C/EBP-β, a member protein of the C/EBP family of transcription factors that have been shown to play a role in the regulation of many mediators of inflammation such as IL-6, interleukin-1α (IL-1α), IL-1β, IL-8, TNFα, granulocyte-colony-stimulating factor, inducible nitric oxide synthase (NOS), lysozyme, hemopexin, haptoglobin, α_1-acid glycoprotein, serum amyloid A1, A2, A3, complement C3, and C-reactive protein (Valeria, 1998), have been found to be significantly elevated in AD cortex compared with non-AD cortex (Rogers, Strohmeyer, Kovelowski, & Li, 2002).

2.2. Astrocytes

Astrocytes are the most common cells in the brain but until recently little has been known about them. Their full functional capacity has not been completely elucidated, however astrocytes are involved with connective tissue and skeletal function of the brain, maintaining the functional integrity of neuronal synapses, and by influencing and/or directing the activity of neurons, and they are thought to play an active role in the function of the brain. When the brain is injured, astrocytes are believed to react by putting down glial scar tissue as part of the healing process.

The role of astrocytes in the inflammatory process associated with AD is more difficult to ascertain. SPs in the AD are known to be associated with reactive astrocytes (Dickson, 1997) and astrocytes cluster at sites of Aβ deposits. They have been shown to secrete many pro-inflammatory molecules, such as interleukins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, complement factors, proteases, and protease inhibitors, similar to and overlapping with that of the microglia (see Table 1).

Electron microscopy of AD brain tissues revealed Aβ in astrocyte processes (Kurt, Davies, & Kidd, 1999). This suggests that astrocytes are involved either with the synthesis or phagocytosis of Aβ. Another study detected a new type of diffuse plaques associated with astrocytes, consisting of Aβ granules, suggesting that astrocytes might be involved in the phagocytosis of Aβ rather than the production of Aβ (Yamaguchi, Sugihara, Ogawa, Saido, & Ihara, 1998). The authors propose that plaque density reaches a plateau when

Table 1
Molecules and products secreted by microglia and astrocytes reportedly associated with AD (McGeer & McGeer, 1995, 2001)

Microglia	Astrocytes
Complement proteins	Complement proteins
Complement inhibitors	Complement inhibitors
Aβ	Aβ
Cytokines and chemokines	Cytokines and chemokines
IL-1	IL-1
TNF-α	TNF-α
IL-6	IL-6
IL-8	IL-8
MIP-1	S100
Reactive oxygen species	COX-2
MHC II	

plaque formation and destruction are equally balanced. Aβ degradation by astrocytes is further supported by research, which showed that mouse astrocytes are able to degrade Aβ in vitro and in situ (Wyss-Coray et al., 2003). This suggests that accumulation of astrocytes around Aβ deposits indicate active phagocytosis of Aβ by astrocytes and that possibly deficits in the clearance of Aβ by astrocytes is part of the pathology of AD. Another study showed that astrocytes accumulate Aβ originating from neuronal origin and that some of these Aβ laden astrocytes can lyse resulting in the formation of amyloid plaques (Nagele, D'Andrea, Lee, Venkataraman, & Wang, 2003). Using three-dimensional reconstruction of SPs in different stages of development it was shown that while microglial cells are the most important factor behind plaque formation, astrocytes are the major factor in plaque degradation (Wegiel, Wang, Tarnawski, & Lach, 2000). While previous studies suggest that astrocytes may play a role in Aβ processing, their main function is thought to be associated with the release of pro-inflammatory products. Astrocytes can be activated by the Aβ to produce chemokines, cytokines, and reactive oxygen species that may cause neuronal cell damage (Johnstone, Gearing, & Miller, 1999; Smits et al., 2002). Under the influence of macrophage released IL-1, astrocytes were found to over-express the cytokine S100B in neuritic plaques (Mrak & Griffin, 2001a). IL-1 and IL-6 were able to induce human astrocytes to over-express the gene for the acute phase protein α_1-antichymotrypsin (ACT) (Nilsson, Das, & Potter, 2001). ACT mRNA was also shown to be expressed at a higher level by astrocytes in the gray matter of AD brains as compared to controls (Pasternack, Abraham, Van Dyke, Potter, & Younkin, 1989) and the ACT was shown to be tightly associated with amyloid plaques in AD brain (Abraham, 2001; Abraham, Selkoe, & Potter, 1988). AD brains were found to have high levels of NOS-positive astrocytes as compared to controls (Simic et al., 2000), suggesting increased production of nitric oxide (NO) in the AD brain. Aβ has been shown to activate cultured astrocytes to produce IL-1β, NOS-mRNA, and NO (Hu, Akama, Krafft, Chromy, & Van Eldik, 1998). Under the stimulation of IL-1α and IL-1β, astrocytes have been shown to produce NO that leads to neuronal damage (Chao et al., 1996). Chemokines released by the astrocytes attract microglia, which further expresses pro-inflammatory products contributing to additional neuronal cell damage.

2.3. Neurons

The neurons themselves seem to play a role in the inflammatory process of AD and have been implicated in the production of inflammatory products. Neurons are able to express significantly higher levels of classical pathway complement protein mRNAs in AD brains as compared to controls (Shen, Li, McGeer, & McGeer, 1997). This has been supported by further research demonstrating neuronal expression of complement proteins and their mRNAs (Akiyama et al., 2000b; Strohmeyer, Shen, & Rogers, 2000; Terai, Walker, McGeer, & McGeer, 1997; Yu, Bradt, & Cooper, 2002). Expression of the pentraxins, C-reactive protein and amyloid P, have been shown to be elevated in AD neurons (Yasojima, Schwab, McGeer, & McGeer, 2000). Neurons are able to produce several cytokines, such as IL-1 (Friedman, 2001; Tchelingerian, Le Seux, & Jacque, 1996), IL-6 (Li, Shen, et al., 2000; Li, Barger, Liu, Mrak, & Griffin, 2000), and TNFα (Liu et al., 1994; Renauld & Spengler, 2002; Tchelingerian, Vignais, & Jacque, 1994; Tchelingerian et al., 1996). The production of these pro-inflammatory products by the neurons may in fact trigger further inflammatory processes that worsen the environment and lead to neuronal toxicity and death.

2.4. The complement system

The complement system is an integral part of the immune system and it plays an important role in the killing of microbes and in the transport and clearance of immune complexes. The complement system is composed of a group of soluble serum proteins, such as C1, C2, C3, C4, C5, C6, C7, C8, C9 and their components, that function as several cooperatively self-regulating cascades or pathways. The classic pathway, an antibody-dependant pathway, is triggered when an antibody (immunoglobulin M or immunoglobulin G) binds to a foreign particle. The alternate pathway constitutes a humoral element of the defense system against infection. It is directly activated by microorganisms and does not require antibodies for activation. Triggering the complement system can result in activation of adhering proteins that act as opsonins of foreign particles

for destruction by phagocytes, direct killing of organisms by forming membrane attack complex (MAC, the terminal cytolytic component of both the classical and alternative pathway) that disrupt the integrity of the organism's membrane, and activation of proteins that act as chemo-attractants for polymorphonuclear leucocytes. Regulation of the complement system occurs via regulator proteins such as factor H, factor I, C4 binding protein, CDS 46, CD59, and C1 inhibitor that keep the system under control.

Over-expression and activation of the complement system has been shown to occur in the Alzheimer's brain (Yasojima, Schwab, McGeer, & McGeer, 1999a). Levels of complement mRNAs for C1r, C1s, C2, C3, C4, C5, C6, C7, C8, and C9 and their resulting protein products were found to be significantly higher in brain areas affected with AD than in the liver of these same individuals. Complement regulators, such as C1 inhibitor and CD59 that protect the host cell against the damage produced by an activated complement system, have not been shown to significantly inhibit complement activation in AD brains (Yasojima, McGeer, & McGeer, 1999). Indeed, research has shown significantly decreased levels of CD59 in the cerebral cortex and hippocampus of AD brains as compared to age control non-AD brains (Price, Kemper, Atkinson, & Morris, 2002; Yang, Konishi, & Shen, 2002). Since CD59 protects host cells against MAC insertion and lysis, ineffective or low amounts of CD59 may allow the MAC to attack and damage unprotected neurons. This would indicate that the inflammatory process causing an increase in the activation of the complement system in the AD brain is not matched by an increase in regulators of the complement system. It may also be that complement regulators are overwhelmed and unable to cope with the increased activation of the complement system.

Activation of the classical complement system in the CNS may not depend on antibodies, as traditionally thought. Evidence has shown that the Aβ can directly bind and activate the classic complement cytolytic pathway in the brain in the absence of antibodies in areas of the brain associated with AD pathology (Bradt, Kolb, & Cooper, 1998; Rogers et al., 1992). This continues to suggest that the Aβ is neurotoxic and contributes to the pathophysiology of AD. C1q, a complement protein, has been shown to bind to fibrillar Aβ, resulting in the activation of the classical complement pathway (Afagh, Cummings, Cribbs, Cotman, & Tenner, 1996; Chen, Frederickson, & Brunden, 1996; Jiang, Burdick, Glabe, Cotman, & Tenner, 1994). C1q has also been shown to be associated with most amyloid deposits in addition to neurons having stained positive for C1q in the AD brain but not in control brains (Chen et al., 1996). Non-C1q activation of the classical activation system by Aβ can also occur via the contact fibrinolysis system (Bergamaschini, Donarini, Gobbo, Parnetti, & Gallai, 2001). The Aβ has been implicated with the induction and formation of the activated C4 and C3 fragment proteins of the classical complement system (Webster, Bradt, Rogers, & Cooper, 1997a). Levels of the MAC, composed of complement proteins C5-9, were found to be elevated in AD brain cortex and were associated with NFTs containing neurons and neuritic plaques but not in non-AD brain cortex (Webster et al., 1997b). Neurons, such as the pyramidal neurons, have been shown to express complement proteins of the classical pathway, C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, and C9 in the AD brain to higher degree than that seen in control non-AD brains (Terai et al., 1997). Tau protein has also been shown to be an antibody-independent activator of the classical complement pathway (Shen et al., 2001).

The alternative complement system is composed of six proteins, C3, factor B, factor D, factor H, factor I, and properdin that perform the function of initiation, recognition, and amplification of the alternative complement pathway. Aβ has been shown to independently activate the alternate complement pathway in a highly specific manner leading to the generation of a cytokine-like C5a complement activation fragment (Bradt et al., 1998). This fragment can then direct the formation of the MAC. The mRNA for the component protein factor B has been shown to be present in the AD frontal cortex and its split products are significantly elevated signifying activation of the alternate complement pathway (Strohmeyer et al., 2000). Interestingly, the major inhibitors of the pathway, factors H and I, were not found to be significantly elevated.

2.5. Chemokines and cytokines

The cytokines are a family of proteins that include the interleukins (ILs), TNFα, and TNFβ. Their production is increased in inflammatory states and they function by regulating the intensity and duration of the

immune response. They are produced by both microglia and astrocytes in the CNS (Hopkins & Rothwell, 1995). Chemokines are a family of small pro-inflammatory cytokine proteins that participate in inflammatory cell recruitment. The chemokines are released by different cells in response to injury and they function by attracting leucocytes to sites of inflammation where they induce cell activation. Both cytokines and chemokines have been shown to be elevated in AD brains (Akiyama et al., 2000a; Moore & O'Banion, 2002; Wilson, Finch, & Cohen, 2002).

Aβ has been shown to increase expression of several cytokine mRNAs (Lee, Nagai, & Kim, 2002). Overexpression of the immune modifying cytokine IL-1 by microglia (Griffin et al., 1989; Griffin, Sheng, Roberts, & Mrak, 1995; Sheng, Mrak, & Griffin, 1997) and astrocytes (Johnstone et al., 1999) has been shown to occur in AD brain. IL-1 manifests properties that include promoting the synthesis and processing of the Aβ precursor protein, enhancing neuronal acetylcholinesterase activity, microglial activation and expression of further IL-1 production, astrocyte activation, and expression of the cytokine S100B by the astrocytes (Mrak & Griffin,2001a, 2001b). S100B is also an inducer of neuronal expression of Aβ precursor protein (Li, Shen, et al., 2000a; Li, Barger, Liu, Mrak, & Griffin, 2000b) and has been shown to be associated with NFTs (Sheng et al., 1997). TNFα, a cytokine produced by microglia that is known to promote cell survival and death in the CNS (Stoll, Jander, & Schroeter, 2000) has been shown to be elevated in AD brain (Fillit et al., 1991; Perry, Collins, Wiener, Acton, & Go, 2001). TNFα has also been shown to increase the production of Aβ (Blasko, Marks, Steiner, Hartmann, & Grubeck-Loebenstein, 1999). On the other hand, TNFα has been reported to have neuroprotective properties (Akiyama et al., 2000a; Tarkowski et al., 2003) in the AD brain, making it difficult to understand the exact role of TNFα in the AD brain. Evidence also points to the involvement of chemokines in the inflammatory process associated with AD brain (Streit, Conde, & Harrison, 2001; Szczepanik et al., 2001). Aβ itself has been shown to induce production of chemokines in macrophages and in astrocytes (Johnstone et al., 1999; Smits et al., 2002).

The genetics of cytokines may play a role in the risk of AD. Different alleles or polymorphisms of a gene maybe associated with increased risk for the disease. The IL-1A 2,2 genotype of the IL-1 gene was noted to confer an increased risk for AD in a group of neuropathologically confirmed AD patients (Nicoll et al., 2000). The study further showed that homozygosity for both IL-1A allele 2 and IL-1B allele 2 was associated with even higher risk, a 10-fold increase, for AD. The IL-1A T/T allele was strongly associated with AD onset before age of 65 in an Italian population, with carriers of this allele showing signs of the disease nine years earlier than carriers of IL-1A C/C (Grimaldi et al., 2000). IL-1B polymorphism was also shown to be associated with AD in a Japanese study (Shibata et al., 2002), with a younger age of onset of AD in an Italian population (Sciacca et al., 2003) and with late onset AD in an Australian study (Hedley et al., 2002). These polymorphisms may lead to overexpression of the gene leading to additional activation of microglia, increased APP production, and increased Aβ deposition (Griffin, Nicoll, Grimaldi, Sheng, & Mrak, 2000). However, other studies contradict the previous findings. No association was found between the IL-1 C/T polymorphism and AD in a Chinese population (Kuo et al., 2003) while another population-based study concluded that it does not seem to be an association between interleukin-1A polymorphism and late onset AD (Fidani et al., 2002). IL-6 polymorphism has been linked to AD (Papassotiropoulos, Hock, & Nitsch, 2001) with one study has showing a delay in the onset and a reduction in the risk of AD associated with the polymorphism in a German population (Papassotiropoulos et al., 1999). Another study looked at polymorphism in the interaction between two cytokines, the pro-inflammatory IL-6 and the anti-inflammatory IL-10, which showed that the co-occurrence of the alleles IL-10A and IL-6C was associated with a higher risk of AD (Arosio et al., 2004). TNFα polymorphism has also been linked to AD in a British and American population study (Culpan et al., 2003) and in a Chinese population study (Ma, Tang, Lam, & Chiu, 2004).

2.6. The Pentraxins

The pentraxins are a family of acute-phase proteins that are involved in many pathologic conditions in the body. Their levels tend to rise significantly following tissue injury or inflammation. The classical pentraxins include the C-reactive protein (CRP) and amyloid

P (AP). CRP and AP are both involved in the innate immune defense system and can activate the classical complement system by an antibody-independent pathway (Elward & Gasque, 2003; McGeer & McGeer, 2001; McGeer, Yasojima, Schwab, & McGeer, 2001; Mold, Gewurz, & Du Clos, 1999; Szalai, Agrawal, Greenbough, & Volanakis, 1997). Both CRP and AP are associated with AD brain lesions (McGeer et al., 2001). AP, a component of all amyloid deposits, has been shown to have widespread association with NFTs and amyloid plaques (McGeer et al., 2001; Yasojima et al., 2000). Originally thought to have been primarily produced in the liver, both CRP and AP have been shown to be generated by pyramidal neurons in the brain and this is up-regulated in the AD brain (Yasojima et al., 2000). Although both CRP and AP have protective functions in the defense mechanisms of the body, they may play a destructive role in the pathogenesis of AD by activating the complement system, leading to cellular and tissue damage in the brain.

3. A possible link between nicotinic acetylcholine receptors and neuroinflammation

A great amount of experimental evidence indicates that several neuronal-type nicotinic acetylcholine receptors (AChRs) are related with the pathophysiology of AD (Auld, Kornecook, Bastianetto, & Quirion, 2002; Wang et al., 2000; reviewed in Zamani & Allen, 2001). On the contrary, the role of AChRs in the AD-related neuroinflammation process is still not very well known.

The possibility of connection between the CNS and the inflammation process has been an object of experimental scrutiny during the last years. However, it was not until now that the details of this relationship were determined (Wang et al., 2003). The basic idea is that the vagus nerve stimulation inhibits TNF release from macrophages, with the subsequent reduction in the inflammatory response. This physiological mechanism is termed "cholinergic anti-inflammatory pathway" because is mediated by the neurotransmitter acetylcholine (ACh) (Borovikova, Ivanova, Zhang, Yang, & Botchkina, 2000). The fact that the competitive antagonist α-bungarotoxin (αBTx) inhibits the ACh-mediated effect suggests that one possible receptor subtype might be the α7 AChR (reviewed in Arias, 2000; Arias, Kem, Trudell, Blanton, 2002). The experimental evidence indicating that electrical stimulation of the vagus nerve inhibits TNF synthesis in wild-type mice but not in α7 subunit-knockout mice strongly supports that conjecture (Wang et al., 2003).

Although the "cholinergic anti-inflammatory pathway" is mainly associated with the systemic inflammation process, a similar regulatory mechanism may occur during AD-induced neuroinflammation. This hypothesis suggests certain role for neuronal-type AChRs in the process of neuroinflammation.

Glial cells of the CNS such as astrocytes, microglias, and O2A-oligodendrocyte progenitors, but not differentiated oligodendrocytes, express several neuronal-type AChR subunits including α3, α4, α5, α6, α7, β2, and β4 (Graham et al., 2002; Nagele et al., 2003; Rogers, Gregori, Carlson, Gahring, & Noble, 2001; Sharma & Vijayaraghavan, 2001; Teaktong et al., 2003; reviewed in Sharma & Vijayaraghavan, 2002). The α7 AChR is the most copious receptor subtype found in astrocytes (Graham et al., 2002, 2003; Hösli, Ruhl, & Hösli, 2000; Hösli, Jurasin, Ruhl, Luthy, & Hösli, 2001; Nagele et al., 2003; Sharma & Vijayaraghavan, 2001; Teaktong et al., 2003). More interesting is the fact that the content of α7 subunits is increased in astrocytes from AD patients when compared with age-matched normal individuals (Teaktong et al., 2003). A possibility is that this is an equilibrium mechanism that helps to maintain the production of TNFα and TNFβ in astrocytes from AD brains at more physiological levels. However, direct evidence supporting this hypothesis has still not been shown.

Functional experiments using hippocampal astrocytes indicated that the expressed nicotinic receptors posses basically the same binding responses as the neuronal-type α7 AChR, but these receptors also behave physiologically in unique ways (Hösli et al., 2000). For instance, AChR stimulation increases intracellular Ca^{2+} ($[Ca^{2+}]_i$) in astrocytes, which in turn triggers Ca^{2+} release from intracellular caffeine-sensitive stores (Sharma & Vijayaraghavan, 2001). Since this stimulation was inhibited by αBTx and methyllycaconitine, two specific competitive antagonists of the α7 AChR, the most plausible receptor subtype is the α7 (reviewed in Arias, 2000; Arias et al., 2002). Nevertheless, the nicotine-mediated $[Ca^{2+}]_i$ increase in O2A-oligodendrocyte progenitors is abolished by

dihydro-β-erythroidin, a competitive antagonist with high specificity for the α4β2 subtype (Rogers et al., 2001), suggesting the involvement of this AChR subtype as well. Additionally, ACh-induced currents were observed in molluscan glial cells, which were inhibited by αBTx, suggesting a α7-like receptor (Hochstrate & Schlue, 1995; Smit et al., 2001). These as well as other experimental results support the idea that astrocytes can be considered an excitable cells, although they act through unique mechanisms including the so-called "Ca^{2+} waves" (reviewed in Perea & Araque, 2002).

The existence of AChRs in non-neuronal cells suggests non-synaptic sources for ACh (Borovikova et al., 2000; Wessler et al., 1997). However, the simplest explanation is based on the fact that ACh diffuses across the extracellular space from neurons to non-neuronal cells (reviewed in Sharma & Vijayaraghavan, 2002). It has been demonstrated that ACh can be released from synapses in hippocampal neurons targeting astrocytes (Araque, Martín, Perea, Arellano, & Buño, 2002; reviewed in Perea & Araque, 2002). The fact that one single astrocyte may envelope many synapses supports this conjecture (reviewed in Perea & Araque, 2002).

On the other hand, molluscan glial cells secrete a hydrosoluble protein called ACh-binding protein (AChBP) (Brejc et al., 2001). A plausible function for the AChBP is to buffer the concentration of ACh in the synaptic cleft. Another additional role might be as a carrier protein, which would permit long-distance diffusion of ACh molecules without being hydrolyzed by acetylcholinesterases. However, the functional importance of the AChBP in the mammalian CNS is still under study.

Although these results suggest the participation of AChRs on the neuroinflammation process, we cannot rule out the involvement of other receptors as well. For example, there is evidence indicating that noradrenergic receptors are also implicated in AD-induced neuroinflammation (reviewed in Feinstein et al., 2002; Galea, Heneka, Dello Russo, & Feinstein, 2003).

4. Role of anti-inflammatory agents

Based on the compelling evidence that inflammatory processes are involved in the pathogenesis of AD, research has looked into the use of anti-inflammatory drugs as a treatment option for patients with AD. Drugs such as the nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid steroids have been studied to determine if they offer any benefits to AD patients.

4.1. NSAIDs

The NSAIDs are a family of drugs that include the salicylate, propionic acid, acetic acid, fenamate, oxicam, and the COX-2 inhibitor classes. They have analgesic, antipyretic, and anti-inflammatory properties and function by inhibiting the cyclooxygenase (COX) enzyme that catalysis the initial step in the conversion of arachidonic acid to several eicosanoids including throboxanes, leukotrienes, and prostaglandins. Eicosanoids play major regulatory roles in cell function including immune and inflammatory functions. The COX enzyme is known to exist as two isoenzymes, COX-1 and COX-2, both of which occur in the brain but whose functions are not well understood. COX-1 is constitutively expressed and is responsible for homeostatic production of prostanoids. COX-2 is inducible in that its expression can be modified depending on the stimuli but may also have a role in the development of homeostasis (Morita, 2002). With the exception of COX-2 inhibitors, all classes of NSAIDs inhibit both COX-1 and COX-2 enzymes. COX-2 inhibitors, as their name implies, selectively inhibit the COX-2 enzyme.

Epidemiological evidence continues to build up indicating that NSAIDs may lower the risk of developing AD (Breitner, 1996; Hoozemans, Veerhuis, Rozemuller, & Eikelenboom, 2003; In't Veld, Launer, Breteler, Hofman, & Stricker, 2002; Mahyar, Gill, Samii, 2003; McGeer, McGeer, Rogers, & Sibley, 1990; McGeer, Schulzer, & McGeer, 1996; Pasinetti, 2002; Rich et al., 1995). Since patients with rheumatoid arthritis and osteoarthritis are typically treated with and are exposed to NSAIDs for a long period of time, epidemiological studies have looked into the association of these diseases and AD. Many of those studies showed an inverse relationship between having arthritis (and being treated with NSAIDs) and AD (Zandi & Breitner, 2001). A prospective population-based study has also shown a significant reduction in the risk of AD in subjects who had taken NSAIDs for a cumulative

period of 24 months or more (In't Veld et al., 2001). Post-mortem studies have also shown the ability of NSAIDs to reduce the inflammation that is consistently seen in AD brain tissue (Mackenzie, 2001). In one post-mortem study, brain tissue from normal individuals with history of chronic NSAID use was compared to a control group without history of chronic NSAID use which demonstrated that while both showed no differences in the amount of SPs or NFTs, the control group had four times the number of activated microglia (Mackenzie & Munoz, 1998), indicating a role for microglia regulation by the NSAIDs. A possible mode of action for the effectiveness of NSAIDs is by the blockage of COX-2 in the brain. It has been shown that COX-2 mRNA and protein are considerably up-regulated in affected areas of AD brain (Pasinetti & Aisen, 1998; Ho et al., 1999; Yasojima et al., 1999b), with COX-2 immunoreactivity noted mainly in pyramidal neurons in the cerebral cortex and the hippocampal formation (Nogawa et al., 2003), suggesting the involvement of COX-2 in AD.

The NSAIDs have been shown to directly affect the production of Aβ through several mechanisms. Ibuprofen, indomethacin, and sulindac sulphide (but not naproxen, celecoxib, or aspirin) were shown to decrease the $A\beta_{42}$ peptide by up to 80% in cultured cells (Weggen et al., 2001). Since not all NSAIDs had this effect, it would seem that this effect occurs through a process that is independent of their anti-inflammatory COX activity. Researchers noted a concomitant increase in the release of the $A\beta_{38}$ isoform suggesting that those NSAIDs reduce $A\beta_{42}$ production be shifting to the production of $A\beta_{38}$. Treatment of mice overexpressing APP with ibuprofen resulted in a reduction of the amyloid plaque load in the cortex along with a reduction of microglial activation in the mice (Yan et al., 2003). A study analyzing the ability of common NSAIDs and the enantiomers of flurbiprofen to lower Aβ levels in neuroglioma cells and in AAP transgenic mice showed that some but not all of the NSAIDs tested lowered the Aβ in cells and were able to reduce the Aβ levels in the mice (Eriksen et al., 2003). The method of Aβ reduction was proposed to occur by shifting γ-secretase (the enzymatic activity by which Aβ is cleaved from APP carboxyl-terminal fragments) to produce the $A\beta_{38}$ isoform instead of the $A\beta_{42}$ isoform. Further research has provided evidence that NSAIDs directly modulate the γ-secretase activity to decrease $A\beta_{42}$ production (Weggen et al., 2003). NSAIDs can also lower the levels of Aβ by inhibiting the protein Rho, a protein that belongs to a family of small GTP proteins that are involved in the regulation of multiple cellular functions (Zhou et al., 2003). Only NSAIDs, such as sulindac sulfide, ibuprofen, and indomethacin (but not naproxen, meloxicam, or piroxicam) that are able to block Rho and its associated kinase were able to lower the levels of Aβ, suggesting that Rho regulates the amount of Aβ production. Neurons that were pretreated with ibuprofen showed decreased production of Aβ upon exposure to the cytokines TNFα and TNFγ as compared to untreated neurons (Blasko et al., 2001). Another study showed that neurons that were treated with COX-1 inhibitors, such as ibuprofen and acetyl salicylic acid, were more resistant to the effects of Aβ than neurons that were treated by COX-2 inhibitors (Bate, Veerhuis, Eikelenboom, & Williams, 2003). The study also showed a decrease in the production of prostaglandin E_2 in the neurons by treatment of both COX-1 and COX-2 inhibitors. Indomethacin has been shown to blunt the stimulation of microglia to Aβ in rats (Netland, Newton, Majocha, & Tate, 1998). NSAIDs may also function by activating (Lehmann, Lenhard, Oliver, Ringold, & Kliewer, 1997) the peroxisomal proliferators-activated receptors (PPARs), a group of nuclear hormone receptors that act to negatively inhibit the transcription of pro-inflammatory genes. PPARα agonists have been shown to inhibit IL-6 and TNFα, and COX-2 expression in cell cultures (Combs, Bates, Karlo, & Landreth, 2001). PPARγ has been shown to inhibit microglial activation and a multitude of pro-inflammatory agents such as cytokines, NOS, and COX-2 (Landreth & Heneka, 2001). Neuroblastoma cells that were stimulated with the pro-inflammatory cytokines IL-1β, IL-6, interferon-α, and interferon-γ to produce Aβ and APP were shown to be reversed by the addition of ibuprofen, indomethacin, or PPARγ agonists (Sastre et al., 2003). The study also showed that ibuprofen and indomethacin were able to regulate β-secretase mRNA levels, expression, and activity and this effect was inhibited by the addition of PPARγ antagonists, suggesting that β-secretase activity is modulated by PPARγ. Another study showed that PPARγ agonists prevented Aβ-stimulated microglial activation and secretion of pro-inflammatory products, microglial-mediated astrocyte proliferation, IL-6

and TNFα expression, and COX-2 expression in cell cultures (Combs, Johnson, Karlo, Cannady, & Landreth, 2000).

Unfortunately, clinical trials of NSAIDs in AD patients have not been very fruitful (Aisen, 2002) and especially disappointing for the COX-2 inhibitors. A recent randomized, double-blind, placebo-controlled trial assessing the effect of the COX-2 inhibitor rofecoxib and the COX-1 and COX-2 inhibitor naproxen versus placebo on AD progression did not slow the cognitive decline of patients with mild-to-moderate AD (Aisen et al., 2003). Among the reasons the authors provide to explain their outcome is that possibly by the time the disease becomes clinically significant, the neuropathology is too advanced for NSAID therapy to be effective. Primary prevention trials of NSAID use in elderly persons without dementia to determine long-term risk reduction in AD are under way (Aisen et al., 2003). Another randomized, double-blind, placebo-controlled trial using the COX-2 inhibitor rofecoxib did not slow the decline of AD (Reines et al., 2004). A study looking into the effect of aspirin COX inhibition on platelet Aβ and APP production did not modify the levels of Aβ or APP in either plasma or serum (Skovronsky, Lee, & Pratico, 2001), suggesting that COX may not be playing a big role in APP secretion. In a study using the anti-inflammatory drug hydroxychloroquine was also shown to be ineffective in slowing down the rate of decline in patients with early AD in a randomized, double-blind, placebo-controlled study (Van Gool, Weinstein, Scheltens, & Walstra, 2001). It is important to note that the primary action of the NSAIDs in AD may not be completely due to their COX inhibitory activity but to their modulatory effects on PPARs, secretase activity, and other mechanisms. Also, not all NSAIDs were shown to be effective in lowering production of Aβ at the cellular level as described above, suggesting that all NSAIDs are not created equally. Specific Aβ-lowering NSAIDs may need to be used in future clinical trials to see if they are as effective clinically. It is possible that NSAIDs may help in reducing the incidence of the disease but may not be as useful once the disease occurs. In other words, they may be able to keep the genie in the bottle but once it is out, there is no putting it back in.

One of the factors preventing the widespread use of NSAIDs to lower the risk of developing AD is the toxicity associated with NSAIDs. NSAIDs are well recognized as having gastrointestinal, renal, hematological, cardiovascular, and CNS toxicity and the elderly population that would benefit from these drugs is also the most susceptible to their toxic side effects. It is usually the gastrointestinal toxicity that gains the most attention since 2–4% of all NSAID users will develop upper gastrointestinal bleeding, symptomatic ulceration, or intestinal perforation each year, making gastrointestinal side effects one of the most common reported side effects related to medication use (Schug, Garrett, & Gillespie, 2003). This toxicity occurs when COX-1, which is involved in cytoprotection of the gastric mucosa via the production of prostaglandin E_2 and prostacyclin, is blocked by NSAIDs, leading to mucosal damage. Since COX-2 is not known to occur in normal gastric mucosa, COX-2 inhibitors are not expected to cause mucosal damage, and COX-2 inhibitors have been shown to cause less mucosal damage than typical NSAIDs (Deeks, Smith, & Bradley, 2002; Mamdani et al., 2002; Schug et al., 2003).

4.2. Glucocorticoid steroids

Steroids are considered to be potent anti-inflammatory agents and function by regulating the transcription of assorted inflammatory molecules, inhibiting the production of enzymes which mediate prostaglandin production, and reducing the expression of cytokines and complement proteins that are pro-inflammatory (Mackenzie, 2001). It is therefore surprising to find that the epidemiologic data for the beneficial effect of glucocorticoid steroid use in the AD brain are either very weak (Hull, Lieb, & Fiebich, 2002; McGeer et al., 1996) or possibly harmful (Gambassi, Landi, & Bernabei, 1997; Harris-White et al., 2001). While glucocorticoids were shown to inhibit Aβ induction of chemokines and cytokines in the CNS (Szczepanik & Ringheim, 2003), a randomized, placebo-controlled trial conducted to determine whether prednisone treatment slowed the rate of cognitive decline in AD patients showed that there was no difference in cognitive decline between the treated group and the control group (Aisen et al., 2000). Indeed, total levels of the glucocorticoid cortisol in the cerebrospinal fluid and serum of AD patients were found to be significantly elevated when compared to non-demented control patients (Ferrari et al., 2000; Peskind, Wilkinson, Petrie, Schellenberg, & Raskind, 2001),

suggesting that increased levels of steroids may be associated with AD.

5. Conclusion

There is too much evidence implicating the involvement of neuroinflammation in AD to be ignored. Yet the role that this neuroinflammation plays in AD is not fully understood. Is neuroinflammation secondary to the AD process or does neuroinflammation directly contribute to it? The results of some of the epidemiologic studies dealing with anti-inflammatory agents suggest that neuroinflammation may play an early role in the pathogenesis of the disease but clinical trials, especially with the COX-2 inhibitors, have been disappointing. Complicating matters is the plethora of participants, from the complement system to nicotinic receptors, implicated in the inflammatory process associated with AD with more yet to be discovered suggesting multiple inflammatory mechanisms involved in the disease. Other issues to consider are that many of the participants in the inflammatory process, such as the microglia and astrocytes, can have both neuroprotective and neurodestructive functions making it difficult to firmly place their role in the disease process. Better understanding of the inflammatory process implicated in AD is needed to improve research in designing therapy specifically targeted against the inflammatory processes. For instance, considering the presented evidence suggesting the involvement of α7-containing AChRs in neuroinflammation, the specific stimulation of this receptor subtype might help to alleviate the neuroinflammatory process found in AD patients.

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