SYSTEMATIC REVIEW

Neuroinflammation in Alzheimer's disease: protector or promoter?

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Abstract

Alzheimer's disease (AD) is an irreversible, progressive and degenerative disorder that destroys the higher structures of the brain. Prominent neuropathologic features of AD are senile plaques, neurofibrillary tangles, synaptic and neuronal loss. There is mounting evidence that chronic inflammatory processes play a fundamental role in the progression of neuropathological changes of AD. It has been shown, that there is a reciprocal relationship between the local inflammation and senile plaques (SPs) and neurofibrillary tangles (NFTs). The major players involved in the inflammatory process in AD are thought to be the microglia and the astrocytes. The process of the activation of glia is characteristized by upregulation or newly expression of a variety of molecules involved in inflammatory response including cytokines, various components of the complement cascade, acute phase reactants, proteases and protease inhibitors, and neurotoxic products. The importance of inflammation in the pathogenesis of AD was indirectly confirmed by epidemiological investigations that revealed a decreased incidence of AD in subjects using anti-inflammatory drugs, especially the non-steroidal anti-inflammatory drugs (NSAIDs). However clinical trials designed to inhibit inflammation have failed in the treatment of AD patients suggesting that anti-inflammatory agents have more protective than therapeutic effect. Despite the ongoing research the extent to which neuroinflammation contributes to disease pathogenesis is still not fully understood. Moreover it is also not clear whether the inflammation in AD brains represent a protective reaction to neurodegeneration or it is rather a destructive process that contributes to further loss of brain function. *(Ref. 117)*.

Key words: Alzheimer's disease, neurodegeneration, neuroinflammation, microglia, immunization, anti-inflammatory therapy.

AD is characterized by a progressive neurodegeneration of the central nervous system. The majority of AD cases correspond to the sporadic form of the disease. Approximately 5–10 % of patients present an autosomal mode of transmission and account for cases called familial Alzheimer's disease (Selkoe, 2001). Prominent neuropathologic features of AD are senile plaques, neurofibrillary lesions, synaptic and neuronall loss, and gliosis (Dickson et al, 1988, Braak and Braak, 1991, West et al, 1994, Gomez-Isla et al, 1996, 1997). The formation of amyloid plaques and neurofibrillary lesions are thought to contribute to the neurodegeneration in the brain of Alzheimer's disease sufferers. In Alzheimer's disease neurofibrillary pathology is present in the form of neurofibrillary tangles, neuropil threads and neuritic plaques (Braak and Braak, 1991). Electron microscopic study revealed that neurofibrillary lesions are composed of paired helical filaments (PHF) (Kidd, 1964). The major constituent of PHF are insoluble, hyperphosphorylated full-length tau species (Lee et al, 1991, Goedert et al, 1992, Grundke-Iqbal et al, 1986b) and truncated forms of tau protein (Novak et al, 1993, 1994). Another important neuropathologic feature of Alzheimer's disease is senile plaque that consists of extracellular deposits of the amyloid ß-peptide (Aß), a 38- to 42-amino-acid fragment of the amy-

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loid precursor protein (APP) (Glenner and Wong, 1984, Masters et al, 1985 a, b). Tau protein and amyloid ß are considered to be key molecules capable to induce the inflammatory processes in the AD brains (Ferencik et al, 2001). Multiple studies provide increasing evidence that inflammation plays an integral role in the development of Alzheimer's disease and may precede plaque and tangle formation. From a therapeutic standpoint it is therefore imperative to identify and understand the role of inflammation in the neurodegenerative cascade.

This article will provide a short overview of the cellular and molecular elements contributing to the inflammatory response characteristic for central nervous system (CNS). We have focused on current insight into the inflammatory hypothesis of AD with particularly emphasis on the anti-inflammatory therapeutic strategies and immunization perspectives.

Neuroinflammation

The brain was regarded as an ‚immune privileged' organ, which was not susceptible to inflammation or immune activation for several reasons. It is devoid of lymph nodes, it is sequestered with a blood-brain barrier, it has a higher tolerance for grafts than other tissues and lower adaptive immune responses. However, it has been shown that immune privilege is not absolute and this dogmatic view has been significantly revised. It is now well accepted, that the brain launches an organized series of innate immune responses, which can take place in the context of disease (Kielian, 2006). Although previously thought that the innate immune response to be a non-specific process engaged by peripheral organs to maintain homeostasis after stress and injury, there is now increasing evidence suggesting that innate immune system utilizes specific mechanism for recognizing the pathogens. The innate immune system is not able to recognize every possible antigen and therefore it focus only on a few highly conserved structures called the pathogen-associated molecular patterns (PAMPs). The cells of innate system expressed family of Toll-like receptors (TLRs) that are able to recognize various exogenous and endogenous PAMPs. It has been already shown that both microglia and astrocytes expressed a variety of TRLs. It was suggested that activation of glial cells via TLRs may serve as an amplification pathway to maximize pro-inflammatory responses within the CNS compartment (DeLeo et al, 2004, Kielian, 2006).

The inflammation associated with the brain, completely differs from that found in the periphery. The classic signs of inflammation such include rubor (redness), tumor (swelling), calor (heat), and dolor (pain) are typically not seen in the brain (Tuppo and Arias, 2005). Neuroinflammation encapsulates the idea that microglial and astrocytic responses in the brain show inflammation-like pattern and that these responses play important role in the pathogenesis of various neurological disorders. This idea came from Alzheimer's disease research, where the contribution of neuroinflammation to the progression of the disease became a topic of scientific discussions (Mrak and Griffin, 2004).

Neuroinflammation in Alzheimer's disease includes a wide spectrum of complex cellular responses such as activation of microglia and astrocytes, cytokines and chemokines release, complement proteins, acute phase proteins, peroxisomal proliferators-activated receptors (PPARs), oxidative injury and related molecular processes (Tuppo and Arias, 2005). The presence of these events underscore the current perception of the brain inflammation as a "double edged sword", with neuroprotective roles for some inflammatory components on one side and detrimental effects on neuronal function on the other side. These interactions may be beneficial as limited "acute phase" reactions, but under chronic conditions may culminate in progressive neurodegeneration (Mrak and Griffin, 2005). Despite the remarkable development in the knowledge about inflammatory response in AD it is still uncertain whether or not activation of brain innate immune system plays a primary or secondary role in mechanisms underlying AD (Praticó and Trojanowski, 2000).

The portrait of microglial cells

The microglia 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 (Streit and Kincaid-Colton, 1995). Microglia, that are composed mostly of mesodermally derived macrophages (Streit and Kincaid-Colton, 1995), constitute approximately 20 % of the total glia cell population (Vilhardt, 2005). Microglia form the first line of defence and are in control of the immune response in the brain. The most characteristic feature of microglial cells is their rapid activation in response to even minor pathological changes in the CNS (Walsch and Aisen, 2004).

Traditionally microglia are divided into two morphologically distinct groups: resting (ramified) and activated (ameboid) microglia (Vilhardt, 2005). The resting microglia have short tortuous processes decorated with small spine-like projections. They migrate to the areas of injury, proliferate and loose their spiny appearance, assuming a swollen form. The activation of microglia leads to the transformation from resident non-phagocytic state into phagocytic state (microglia-derived brain macrophages). The activated microglia develope enlarged cell processes which give the cells a bushy appearance (Streit et al, 1999). Microglia activation is a key factor in the defence of the neural parenchyma against infectious diseases, trauma, ischaemia, tumours and neurodegeneration. Activation of microglia displays a repertoire in terms of proliferation, migration to the site of injury, characteristic morphological, immunophenotypical (upregulation of innate immune cell surface receptors, MHC antigens) and functional changes (antigen-presenting cell capabilities). They are capable of releasing several potentially cytotoxic substances *in vitro,* such as reactive oxygen intermediates (ROI) or species (ROS) and reactive nitrogen intermediates (RNI), proteases, arachidonic-acid derivates, excitatory amino acids, quinolinic acid and pro-inflammatory mediators such as prostaglandins, TNF-α, IL-1ß, and chemokines. Microglia activation often precedes reactions of any other cell type in the brain. They respond not only to changes in the brain's structural integrity but also to very subtle alterations in their microenvironment, such as imbalances in ion

homeostasis that precede pathological changes that are detectable histologically (Kreutzberg, 1996, Vilhardt, 2005).

It is worth mentioning that microglia may undergo ageing-related changes in the cell morphology and surface antigen expression (Conde and Streit, 2006). During aging, microglia become progressively more activated, and by mid-life many microglia cells develope extensively ramified cellular processes (Rozemuller et al, 2005). Later, the number of enlarged, and especially phagocytic, microglial subtypes increase (Sheng et al, 1998). At this stage, microglial hypertrophy may become extreme, they loose contact inhibition and begin to fuse into microglial clusters (Streit et al, 1999). Furthermore, senescence of the innate immune system can be associated with a pro-inflammatory status of glial cells. On the other hand, age-related increases in the number of activated microglia are small compared to the microgliosis of Alzheimer's disease (Mrak and Griffin, 2005).

Recently several studies showed that activation of microglia are a relatively early pathogenic event that precedes the process of severe destruction of the brain parenchyma in AD patients. During the disease progression, activated microglia are scattered throughout affected regions of the cerebral cortex, and focally they are concentrated in Aß plaques. Plaque-associated microglia is considered as an important element in the transformation of early diffuse amyloid deposits into the late neuritic Aß plaques (Mrak and Griffin, 2005). Several researchers have described the ability of microglia to phagocytose and internally degrade Aß deposits. This process is considered to be important for plaque evolution (Moore and O'Banion, 2002). Microglia associated with senile plaques also express activation markers, such as major histocompatibility complex (MHC) class I and class II molecules and integrins as well as Fc receptors (Blasko et al, 2004). Following activation, microglial cells also produce acute-phase proteins, complement components, cytokines and chemokines (Blasko and Grubeck-Loebenstein, 2003). Moreover, microglia can express scavenger receptors that mediate adhesion of the microglia to Aß fibrils leading to secretion of reactive oxygen species (El Khoury et al, 1996), that result to the damage of neurons via the free radical oxidative damage pathway (Tuppo and Arias, 2005).

Activated microglia are also present in and around neurofibrillary tangles even at early stages of tangle formation (Sheng et al, 1997). At the later stages the regional distribution of microglia parallels that of tangle self distribution and activated microglia have been correlated with increased number of NFT (Overmyer et al, 1999, Sheffield et al, 2000). These studies collectively support the concept that inflammation mediated by microglia is an important component of AD pathophysiology (Benveniste et al, 2001).

A portrait of astroglial cells

Astrocytes were first identified in 1856 by Virchow, who proposed that they have a metabolic and structurally supportive role for the neurons (Laming et al, 2000). Astrocytes are the most common cells in the brain (Raivich et al, 1999), constituting approximately 85% of glia population (Gahtan and Overmier, 1999). They are large star-shaped cells which numerous processes extend into the surrounding neuropil. When the brain is injured, astrocytes are believed to react by putting down glial scar tissue as part of the healing process (Tuppo and Arias, 2005). When neurons die, microglia remove the dead cells by phagocytosis. The damaged area is then repaired by proliferation of astrocytes, which fill the defect and form an astrocytic scar (Ridet et. al, 1997, Fawcett and Asher, 1999). Reactive gliosis – the process of the glia activation, occurs during various neurological injuries including Alzheimer's disease and related neurodegenerative diseases (Eng et al, 1992). Characteristic feature of reactive gliosis is the hypertrophy of astrocytes and the proliferation of microglia and astrocytes (Eddleston and Mucke, 1993, Ridet et al, 1997). Activated astrocytes show both neuroprotective and neurotoxic properties (Gahtan and Overmier, 1999). The formation of a glial barrier around a lesion isolates the still intact CNS tissue from secondary lesions (Ridet et al, 1997, Raivich et al, 1999). Although reactive gliosis has long been considered as the major obstruction to axonal regeneration after an injury, some data suggest that in certain conditions reactive astrocytes may provide a substrate for axonal re-growth (Ridet et al, 1997). Another typical feature of reactive astrocytes is increased expression of a large array of various molecules. Astrocytes similar to microglia have been shown to secrete many pro-inflammatory molecules such as interleukins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, complement components and factors, proteases and inhibitors of proteases (Tuppo and Arias, 2005). In addition, reactive astrocytes showed increased expression of MHC II and at the lesser extend also MHC I antigens, cellular adhesion molecules and cytotoxic oxygen and nitrogen free radicals. The presence of MHC antigens on astrocytes indicates that astrocytes may activate T lymphocytes. Increased expression of cellular adhesion molecules by astrocytes might promote brain inflammation by increasing transport of immune cells through the blood-brain barrier (Gahtan and Overmier, 1999).

In the brain of AD patients activated astrocytes are integral and prominent components of Aß senile plaques (Griffin and Mrak, 2005). Reactive astrocytes are present in virtually all diffuse plaques, but the highest densities of these cells are in the neuritic plaques (Mrak et al, 1996; Akiyama et al, 2000). Astrocytic overexpression of the neurotrophic signaling molecule S100ß in the neuritic plaques correlates with the degree of neuritic pathology in Aß plaques (Sheng et al, 1997, Mrak and Griffin, 2001). Processes of astrocytes are seen to point in a radial direction towards the centre of the senile plaque. The dense-core plaques astrocytes is outlined by tangentially running astrocytic processes. It is suggested that the astrocytosis is not simply reactive to other primary events occuring within the plaques, but is itself active in the pathogenesis and morphogenesis of the senile plaque (Mrak et al, 1996). Futhermore, astrocytes may also impair the natural ability of microglia to clear plaques. If the Aß is first exposed to astrocytes, they deposit proteoglycans that greatly inhibit the microglial attack (DeWitt et al, 1998; Shaffer et al, 1995).

Complement system

The complement system is composed of of more than 35 plasma soluble and cell-bound proteins that function as several cooperatively self-regulating cascades or pathways. Complement activation is leading to chemotaxis, opsonization, immune clearance, cytolysis, inflammation and the processing of immune complexes. The main source of these proteins in peripheral blood is liver, but they are also synthesized in other organs including the brain. In the brain complement proteins are synthesized by neuronal cells, microglia, astrocytes, oligodendrocytes, and endothelial cells (Barnum, 1995).

Generally there are three complement pathways: the classical, alternative, and lectin-mediated cascades. The classical pathway, an antibody dependant pathway, is triggered by activation of the C1-complex via binding to antibodies complexed with antigens. The alternative pathway constitutes the humoral component of natural defence system against infection without antibody participation. Full activation results in the generation of C5b-9, the "membrane attack complex" (MAC), that disrupts the integrity of the target cell membrane causing lysis and cell death and formation of complement components fragments that act as chemo-attractants for polymorphonuclear leucocytes (Loeffler, 2004).

Over-expression and activation of the complement system has been shown to occur also in the Alzheimer's brain. Both mRNA expression and protein synthesis of native complement components are increased in the AD brain (Walker and McGeer, 1992, Shen et al, 1997, Yasojima et al, 1999a). The presence of activated early complement components (Eikelenboom and Stam, 1982, Ishii and Haga, 1984, Veerhuis et al, 1996) and of the MAC, composed of complement proteins C5b-9 (Itagaki et al, 1994, Lue et al, 1996, Webster et al, 1997 a), has been demonstrated to be elevated primarily in regions containing extensive pathology (e.g., the hippocampus and cortex) and were associated with NFTs containing neurons, dystrophic neurites and neuritic plaques, but not in non-AD brain cortex (Webster et al, 1997 b).

There is convincing evidence for activation of both the classical and alternative pathways, resulting in full activation as indicated by the presence of the MAC. Activation of the classical complement pathway in the CNS may not depend on antibodies, as traditionally thought. Evidence has shown that the Aß can directly bind complement component C1 and initiate the classical complement cytolytic pathway in the brain in the absence of antibodies in areas of the brain associated with AD pathology (Rogers et al, 1992, Bradt et al, 1998). This in turn may play a key role in activation of microglia and production of proinflammatory cytokines. These mediators may induce Aß secretion creating vicious cycle (Walsch and Aisen, 2004). Thus, the senile plaques of AD are a unique activator of complement. In addition, the complement cascade can be activated by the pentraxins, amyloid P (AP) and C-reactive protein (CRP), which are upregulated in affected regions of AD brain (McGeer and McGeer, 2003).

In the AD brain complement activation was initially thought to be limited to the classical pathway. However several reports have indicated increased concentrations of activated factors Bb and Ba, and a regulatory factor H of the alternative pathway, in the AD brain (Strohmeyer et al, 2000, 2002). Because complement activation generates both neuroprotective and neurotoxic effects, the significance of increased complement activation in the development and progression of AD is unclear (Loeffler, 2004).

There are protective mechanisms that defend host cells against spurious activation of complement and against self-damage when complement is activated. These include C1 inhibitor, C4bp, DAF, membrane cofactor protein (CD46) and protectin (CD59). The most important is CD59 since it directly protects against MAC insertion into host cell and thus inhibits bystander lysis. The mRNAs for complement components are sharply up-regulated in affected regions of AD brain, but those for C1 inhibitor and CD59 are not (McGeer and McGeer, 2003). Thus, there is no compensatory up-regulation of inhibitors to protect host brain tissue in AD.

Cytokines and chemokines

The cytokines are a family of hormone-like proteins or glycoproteins that regulate the immunity, inflammation, and hematopoiesis. The major classes of cytokines are the interferons (IFNs), interleukins (IL), tumor necrosis factors (TNFs), transforming growth factors (TGFs) and colony stimulating factors (CSFs). Chemokines are a family of small pro-inflammatory chemotactic 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 (Tuppo and Arias, 2005). Among them, extensively studied in relation with AD onset or progression were mainly: pro-inflammatory cytokines interleukin-1 alpha and beta (IL-1α, IL-1ß), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and transforming growth factor beta (TGF-ß) together with chemokines IL-8, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 (MIP-1α, MIP-1ß) (Mrak et al, 1995, McGeer and McGeer, 2003; Cacquevel et al, 2005).

Interleukin-1 (IL-1) has been implicated in a number of neurodegenerative conditions and is generally believed to have neurotoxic actions, although the mechanisms of these effects are unclear (Lucas et al, 2006). There are two molecular forms (IL-1α and IL-1ß), that is secreted by microglia and astrocytes. IL-1 produced by activated microglia may trigger production of other cytokines, such as IL-6, TNF-α by astrocytes and other cells. Furthermore, IL-1 induces astrocytes and neurons to produce more ß-amyloid which leads to deposition of amyloid fibrils (Griffin et al, 1995, Nilsson et al, 1998). Through various pathways, IL-1 causes neuronal death, which activates more microglia, which in turn releases more IL-1 in a self-sustaining and self-amplifying fashion.

Interleukin-6 (IL-6) is a multifunctional cytokine that stimulates the acute-phase reaction, which enhances the innate immune system and protects against tissue damage. IL-6 is synthetised by microglia, astrocytes, neuronal and endothelial cells. In certain condition, IL-6 may have inflammatory or immunosuppressive effects (Ferencik et al, 2001). IL-6 seems to act as a secondary process amplifying the inflammatory response initiated by IL-1ß (Lee et al, 1993). Elevated levels of IL-6 mRNA were demonstrated in the entorhinal cortex and the superior temporal gyrus of AD patients (Ge and Lahiri, 2002, Lahiri et al, 2003).

Tumor necrosis factor-α (TNF-α; 17 kDa) is believed to trigger programmed cell death in the perifery (Venters et al, 2000), while within CNS may have neuroprotective effect (Ferencik et al, 2001). It has been shown that TNF-α may be a potent stimulator of several neuronal survival factors including manganese-superoxide dismutase and Bcl-2 (Blasko and Grubeck-Loebenstein, 2003). In the brain TNF-α may mediate synaptic scaling in response to prolonged blockade of activity (Stellwagen and Malenka, 2006). Synaptic scaling is a compensatory homeostatic mechanism by which the brain maintains the stability of neural circuits (Hubka, 2006) and prevents the catastrophic amnesia associated with synapse loss. Under conditions where synaptic scaling does not occur, a loss of synapses can lead to memory loss once a critical number of synapses is reached. However, with synaptic scaling, memory loss is more gradual, with more recent, less established memories being the first to be lost. This is very similar to the pattern of retrograde amnesia that is characteristic for Alzheimer's disease (Small, 2004). Increased levels of TNF-α in Alzheimer's disease may represent compensatory mechanism of the brain against progressive synaptic loss.

Members of the transforming growth factor ß (TGF-ß) superfamily, are characterized as pleiotropic cytokines that orchestrate many physiological and pathological processes (Vivien et al, 1998, Ebendal et al, 1998). In Alzheimer's disease, several data show that TGF-ß is increased in the brain of patients. It has been shown that increased levels of TGF-ß correlated with the degree of cerebral amyloid angiopathy observed in AD brains (Wyss-Coray et al, 1997). Moreover, TGF-ß was also found in senile plaques and in neurofibrillary tangles (Van der Wal et al, 1993).

A finding of particular interest is that the risk of AD seems to be substantially influenced by several polymorphisms in the non-coding regions of genes encoding these inflammatory cytokines. Those alleles, which favour increased expression of the inflammatory mediators, are more frequent in AD than in controls. It is notably documented in the case of IL-1α which seem to be a genetic factor for AD (Rainero et al, 2004).

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. Evidence favouring the concept of therapeutic strategies directed at reducing the level of inflammation was based on the postmortem examination of the brain tissue of patients who had been using traditional non-steroidal anti-inflammatory drugs (NSAIDs) showing significantly fewer activated microglia than non-users (Makenzie, 2000). In accord with these findings several drugs such as the NSAIDs and glucocorticoid steroids have been studied to determine if they offer any benefits to AD patients.

The NSAIDs are a family of drugs that include the salicylate, propionic acid, acetic acid, fenamate, oxicam, and the cyclooxygenase 2 (COX-2) inhibitor classes that are widely used as treatments for a variety of inflammatory conditions, particularly arthritis. NSAIDs are the most thoroughly documented COX inhibitors and have been used as therapeutic agents since 1899 (Tegeder et al, 2001). NSAIDs are widely used agents, a number of which are available as non-prescription drugs. With the exception of selective 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.

The modus of drug action is based on the inhibition of 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. It has been emphasized in the literature that a constitutive enzyme COX-1 plays an important role in basal physiological functions (Marnett et al, 1999; Shanmugam et al, 2003), while COX-2 is normally expressed at low levels and its expression is induced by inflammation (Vane et al, 1998). COX-2 is rapidly induced in response to brain injury and thus is the most appropriate target for anti-inflammatory action. But this is an oversimplification which is inappropriate for brain. COX-2 is constitutively expressed at high levels in brain, especially in pyramidal neurons that are vulnerable to neurodegenearation (Yasojima et al, 1999b). On the other hand, COX-1 is not constitutively expressed in brain at high levels (Seibert et al, 1994) and is upregulated in activated microglia (Hoozemans et al, 2002). Until now, COX-2 has not been detected in astrocytes and microglia in AD and is barely induced by the inflammatory mediators in AD. Therefore, it can be anticipated, that NSAIDs with inhibitory activity against COX-1 rather than COX-2 would be more likely to reduce brain inflammation selectively (McGeer and McGeer, 2006).

Epidemiological evidence indicates that NSAIDs may lower the risk of developing AD (Tuppo and Arias, 2005). Since patients with rheumatoid arthritis and osteoarthritis are usually treated with NSAIDs for a long period of time, epidemiological studies have looked into the association of these diseases and AD. Many of those studies have reported an inverse relationship between having arthritis (and being treated with NSAIDs) and AD (Zandi and Breitner, 2001) but not with vascular dementia (McGeer and McGeer, 2006). The authors, therefore, concluded that the anti-inflammatory drugs may delay the onset as well as slow the progression of Alzheimer's disease.

Unlike promising results coming from small scale trials, later large scale clinical studies of NSAIDs in AD patients have been disappointing. Randomized controlled trials assessing the effect of the COX-2 inhibitor (rofecoxib and celecoxib) and the COX-1 and COX-2 inhibitor (naproxen) failed to demonstrate any beneficial effect on cognition, behavior or activities of daily livings of Alzheimer's disease patients (McGeer and McGeer, 2006). Among the reasons of failure of anti-inflammatory therapies is that possibly by the time the disease becomes clinically significant, the neuropathology is too far advanced for NSAID therapy to be effective. It may be necessary to initiate treatment with anti-inflammatory drugs before clinical manifestation of the disease appears (Walsch and Aisen, 2004). The inconsistent results between NSAID trials suggest that neuroprotection may be the result of mechanisms other than the inhibition of COX, such as inhibition of Aß formation and aggregation, decrease of the production of nitric oxide and pro-inflammatory cytokines, decreased secretion of Aß peptides and soluble APP and PPAR-gamma agonism (Blasko and Grubeck-Loebenstein, 2003, McGeer and McGeer, 2006; Sastre et al, 2006). The critical point to the neuroprotective effect of NSAID seems to be timing and duration of therapy.

The peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is a potential downstream target for some NSAIDs. They include ibuprofen, indomethacin and naproxen that belong among the five most prescribed NSAIDs, which potentially decreased the risk for AD (Lehman et al, 1997; In't Veld et al, 2001). PPAR-gamma represents ligand-activated transcription factors that belong to a nuclear receptor superfamily. Its activation results in the inhibition of various inflammatory events, such as the production of IL-1ß, TNF-α, IL-6 and inducible nitric oxide synthase (iNOS) in macrophages and microglia. Activation of PPAR-gamma can be performed by the endogenous ligand prostaglandin J2 or by NSAIDs and drugs of the thiazolidinedione class which are able to inhibit the ß-amyloid stimulated secretion of proinflammatory products of microglia and monocytes responsible for neurotoxicity and astrocyte activation (Combs et al, 2000). Activation of PPAR-gamma also decreases Aß levels. According to recent findings, there is 40 % reduction in PPAR-gamma protein levels in AD patients compared with controls (Sastre et al, 2006). On the other hand, several polymorphisms in PPARs have been implicated as a risk factor for AD. This indicates that PPAR-gamma may be a major factor for the regulation of amyloidogenic pathways. Therefore, the PPAR-gamma agonists may be probably used for the treatment of AD. These drugs are already in use as clinical treatment for type II diabetes.

Recently, it was proposed that some NSAIDs might activate the peroxisome proliferator-activated receptor-gamma (PPAR-gamma). PPAR-gamma belongs to a family of nuclear receptors that are able to regulate the transcription of pro-inflammatory molecules, such as iNOS. The activation of PPAR-gamma has been recently reported to reduce Aß levels in cell culture and AD animal models. The implication of PPAR-gamma in the control of Aß-induced inflammation suggests a new target for AD therapy and emphasizes the contribution of neuroinflammatory mechanisms to the pathogenesis of AD.

Immunotherapy via active and passive immunization

Immunotherapy approaches in Alzheimer's disease and related disorders represent alternative therapeutic strategies that may offer genuine opportunities to modify disease progression. In 1999 Schenk and his colleagues reported that repeated immunisation of transgenic ßAPP mice with ß-amyloid as antigen led to the production of Aß antibodies and could halt or even reverse accumulation of ß-amyloid deposits in the brain of these mice (Schenk et al, 1999). The immunization resulted in the significant inhibition of neuritic dystrophy and astrogliosis and active clearance of Aß by microglial cells (Schenk et al, 2004, Solomon, 2004). Strikingly, immunotherapy reversed cognitive decline in the mouse models of familial Alzheimer's disease (Morgan et al, 2000, Hock et al, 2003, Dodel et al, 2004).

Based on these exciting results, the first clinical trials in which AD patients were immunised with Aß 42 in its fibrillary form (AN1792) were started. The vaccine was well tolerated in phase I of the trial. However the clinical trial was halted during phase IIa, because 6 % of the 372 vaccinated Alzheimer's disease patients developed the aseptic subacute meningoencephalitis (Blasko and Grubeck-Loebenstein, 2003, Solomon, 2004, Gelinas et al, 2004). Post-mortem examination of brains from two patients who suffered from meningoencephalitis revealed the presence of CD4+ T lymphocyte infiltration in the leptomeninges and in cerebrovasculature in the area enriched with amyloid angiopathy and in the perivascular spaces of cerebral isocortex (Nicoll et al, 2003, Ferrer et al, 2004). Analysis of these case reports has provided support for the theory that the adverse response to the vaccine was due to a T cell-mediated autoimmune response (Agadjanyan et al, 2005).

In transgenic animals active immunization with Aß resulted in clearance of plaques and lessening of cognitive decline. The question remains to be answered whether similar findings might be seen also in AD patients receiving Aß immunotherapy. In few cases reported to date, there were some isocortical regions devoid of plaques, dystrophic neuritis and reactive astrocytes in immunized AD patients (Gelinas et al, 2004, Schenk et al, 2004). On the basis of these findings it was concluded that immunization might result in the plaque clearance. This provided hope for prospective immunotherapeutic approaches in the future.

Passive immunization has also been successful in animal models. The application of peripherally administered antibodies to Aß was sufficient to reduce amyloid burden in the brain despite the low penetration of antibodies into the CNS (Bard et al, 2000, 2003). The results of these studies clearly showed, that Aß-specific antibodies bind to Aß peptides in the brain and in the periphery, thus lowering the load of Aß (Blasko and Grubeck-Loebenstein, 2003). The mechanism of the plaques clearance appears to be depended on the Fc receptor-mediated phagocytosis. On the other hand, it has been already reported that the injection of the F(ab')2 fragment of antibody or single chain antibody against Aß led also

to the clearance of amyloid deposits in AD mice models. These findings suggest that additional mechanism independent of Fc interactions may be involved in the process of plaque clearance (Bacskai et al, 2002, Schenk et al, 2004, Fukuchi et al, 2006).

The passive immunotherapy of APP-transgenic mice prevented age-associated cognitive decline in the APP-transgenic mice even before there was any detectable decrease in cerebral amyloid plaque numbers (DeMattos et al, 2001). In summary, the passive immunization with anti-Aß antibodies has the potential to be effective in those AD patients who do not mount a significant antibody response (Weksler, 2004).

Conclusion

As highlighted in this review, a complex of inflammatory components include brain cells such as microglia and astrocytes, the classic and alternate pathways of the complement system, as well as cytokines and chemokines have been identified as playing potential roles in AD pathogenesis. However it is still not clear whether inflammation has a damaging or beneficial effect on the brain. A better understanding of the inflammatory process implicated in AD is needed to improve research in designing therapy specifically targeted against the inflammatory processes. The inflammatory hypothesis of Alzheimer's disease, which predicts that anti-inflammatory drugs may have beneficial effects on the disease progression of AD, has been extensively investigated in clinical studies and in basic research during the last 20 years. This notion was bolstered by epidemiological studies suggesting that neuroinflammation may really play an important role in the pathogenesis of the disease and might be a relevant drug target for AD therapy. Unfortunately, clinical trials, especially with the COX-2 inhibitors, have been disappointingly negative and due to its failure, the relevance of COX and their products becomes more and more questionable. On the contrary, the follow-up research provided more evidence that both active and passive Aß immunisation decrease the load of senile plaques and reduces cognitive impairment in animal models of Alzheimer's disease. Although the first clinical trial of active immunisation with synthetic Aß was suspended after several patients experienced meningoencephalitis, the following analysis revealed a powerful effect of vaccination in the clearance of amyloid plaques from the human cerebral cortex. In future, combination of safe and effective imunization scheme with anti-inflammatory therapeutic strategies may offer prospective alternatives for existing treatment of Alzheimer's disease.

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