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Review article

Inflammatory processes in Alzheimer's disease

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Abstract

Generation and deposition of amyloid beta peptides and neurofibrillary tangle formation are key mechanisms involved in AD pathogenesis. Recent evidence suggests that inflammatory mechanisms represent a third component which, once initiated by degeneration, may significantly contribute to disease progression and chronicity. Various neuroinflammatory mediators including complement activators and inhibitors, chemokines, cytokines, radical oxygen species and inflammatory enzymes are generated and released by microglia, astrocytes and neurons. Degeneration of aminergic brain stem nuclei such as the locus ceruleus and the nucleus baslis of Meynert may facilitate the occurrence of inflammation in their respective projection areas given the antiinflammatory and neuroprotective action of their key products norepinephrine and acetylcholine. While inflammation has been thought to arise secondary to degeneration, recent experiments demonstrated that inflammatory mediators may stimulate APP processing by upregulation of beta secretase 1 and therefore are able to establish a vicious cycle. Despite the fact that some aspects of inflammation may even exert protective effects to bystander neurons, antiinflammatory treatment strategies should therefore be considered. Non-steroidal antiinflammatory drugs have been shown to reduce the risk and delay the onset to develop AD. However, the precise molecular mechanism underlying this effect is still being debated. Several mechanisms including inhibition of cyclooxygenase 2, gamma secretase or activation of the peroxisome proliferator activated receptor gamma may alone or, more likely, in concert account for the epidemiologically observed protection.

Keywords: Neurodegeneration; Innate immunity; Microglia; Astrocyte; Amyloid; Cytokine

Contents

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1. Alzheimer's disease

As the most common neurodegenerative disorders, Alzheimer's disease (AD) currently affects 20 to 30 million individuals worldwide (Selkoe, 2005). AD accounts for most cases of dementia that are diagnosed after the age of 60 years of life. In the US, the number reaches roughly 4 million patients. The prevalence of AD increases with age, affecting approximately 1% to 3% of the population in the 6th decade of life, 3% to 12% of the population between 70 and 80 years, and up to 25 to 35% older than 85 years (Walsh and Selkoe, 2004). Because life expectancy has been constantly increasing in industrialized countries, it is predicted that the incidence of AD will increase three fold over the next 50 years.

Typically, AD starts with mild memory deficits, primarily affecting short term memory and gradually progresses to severe dementia and stupor. The earliest symptoms often appear as subtle, intermittent deficits in remembering minor events of everyday life, such as forgetfulness and difficulties recalling new names or recent conversations, referred to as loss of episodic memory. At later stages, a profound dementia develops affecting multiple cognitive and behavioral spheres. The patient is unaware of time and place, and, at times, cannot identify even close family members. These symptoms are frequently accompanied by additional neurological symptoms such as extrapyramidal motor signs, slowed movements and hampered motor coordination. Death occurs, on average, 9 years after the initial clinical diagnosis and is usually caused by respiratory complications, such as aspiration or pneumonia.

At autopsy, the brain of a typical AD patient reveals a macroscopically visible cerebral atrophy involving brain regions implicated in learning and memory processes, including the temporal, parietal and frontal cortex as well as the hippocampus and amygdala. This brain volume reduction is due to a profound degeneration of neurons and synapses (Mattson, 2004). AD brains show two characteristic lesions: extracellular deposits of β-amyloid peptides, so-called neuritic or senile plaques, and intracellular neurofibrillary tangles of hyperphosphorylated tau (Lee et al., 2001; Selkoe, 2003).

Toxic β-amyloid peptides (Aβ) are generated by the sequential action of two proteases denoted as β-secretase (BACE1) and γ-secretase, which cleave the amyloid precursor protein (APP). Aβ exists with different carboxyl endings, from which $A\beta_{1-40}$ and $A\beta_{1-42}$ appear to be the major subtypes deposited in the brain. Aβ peptides can also be detected in normal cerebrospinal fluid and in conditioned media from various tissue culture cell lines (Haass et al., 1992; Seubert et al., 1992; Shoji et al., 1992), suggesting that it is constantly produced and constitutively secreted. The importance of Aβ formation was revealed by dominantly inherited familial forms of AD that are linked to APP mutations around the β- and γ-secretase cleavage sites (Hardy and Allsop, 1991). These findings resulted in the generation of transgenic mouse models of cerebral amyloidosis and AD-like histopathology, i.e. amyloid plaques and cerebral amyloid angiopathy (CAA) (Hsiao et al., 1995; Sturchler-Pierrat et al., 1997; Lamb et al., 1999; Moechars et al., 1999; Van Dorpe et al., 2000).

Neurofibrillary tangles (NFTs) constitute intraneuronal cytoplasmic accumulations of non-membrane-bound bundles of paired helical filaments, consisting of hyperphosphorylated tau. Tau is also found in dystrophic neurites. It is present in aggregates conjugated with ubiquitin, a property shared with other aggregating intraneuronal proteins, such as α-synuclein. Importantly, Aβ deposits as well as neurofibrillary tangles can also be found in other neurodegenerative diseases, even in brains of patients without any history of cognitive or other neurological deficits (Lee et al., 2001), suggesting the contribution of additional factors to establish the disease.

The eventual deposition of Aβ and neurofibrillary tangle formation may not account for all clinical symptoms of AD, particularly the earliest clinical symptoms arising before neuronal degeneration is evident. Inflammatory changes are observed in AD brain overall, particularly at the amyloid deposits, which are rich in activated microglia. Once stimulated, the microglia releases a wide variety of pro-

inflammatory mediators including cytokines, complement components, various free radicals and nitric oxide (NO), all of which potentially contribute to further neuronal dysfunction and result eventually in cell death. These mediators create and feed a vicious cycle that could be essential for the pathological progression of AD (Griffin et al., 1998; Griffin, 2000).

2. Inflammation and AD

Although Aβ has been considered to play a key role in AD pathogenesis (Walsh et al., 2002b; Walsh and Selkoe, 2004), it remains still uncertain whether Aβ plaques and neurofibrillary tangles are causative for AD. These doubts are fueled by the finding that the Aβ plaque burden poorly correlates with the progression and severity of dementia in AD. Moreover, transgenic animals that develop widespread Aβ plaque deposition in response to overexpression of APP mutations show only slight cognitive deficits (Braak and Braak, 1998; Davis and Laroche, 2003). Furthermore, formation of neurofibrillary tangles may correlate better with the decline in cognitive skills, but seem to occur as a late event downstream of Aβ accumulation. However, some experimental evidence indicates that protofibrils and oligomers of $A\beta_{1-40}$ and $A\beta_{1-42}$, rather than Aβ plaques, contribute to early dendritic and synaptic injury and thereby to neuronal dysfunction (Walsh et al., 2002a).

In addition to these direct toxic effects, Aβ may also promote neurodegeneration by parallel mechanisms including the activation of microglial cells and astrocytes. The induction of a microglia-driven inflammatory response results in the release of various inflammatory mediators including a whole array of neurotoxic cytokines (Akiyama et al., 2000; Tan et al., 1999). Once activated, microglia cells may also recruit astrocytes that actively enhance the inflammatory response to extracellular Aβ deposits. This neuroinflammatory component of AD is further characterized by a local cytokine-mediated acute-phase response, activation of the complement cascade and induction of inflammatory enzyme systems such as the inducible nitric oxide synthase (iNOS) and the prostanoid generating cyclooxygenase-2 (COX-2). Several lines of evidence suggest that all of these factors can contribute to neuronal dysfunction and cell death, either alone or in concert (Abbas et al., 2002; Bezzi et al., 2001; Brown and Bal-Price, 2003).

This review will discuss several aspects of neuroinflammation in AD focusing on the following questions:

(1) What stimulates the inflammatory reaction in the AD brain?
(2) Which cells contribute to the inflammatory component of AD and how do they interact?
(3) Which pro- and antiinflammatory mediators are being released in the AD brain, and what is their supposed mechanism of action?
(4) Are there any known pathogenetic factors in the AD brain that may facilitate the induction and persistence of neuroinflammatory mechanisms?
(5) Is neuroinflammation just a reaction to neurodegenerative events or does it act on neurodegenerative pathomechanisms thereby establishing a vicious and self-perpetuating cycle?
(6) Can antiinflammatory treatment strategies serve as a future AD therapy?

3. Immunostimulators in Alzheimer's disease

While minor signs of neuroinflammation can be found in the normal aging brain, the AD brain faces a much stronger activation of inflammatory systems indicating that an increasing amount or qualitatively different immunostimulants are present. Cumulative evidence suggests that Aβ peptides play a pivotal role as inducers of neuroinflammation. However, chromogranin and several other proteins may contribute to this induction.

3.1. Amyloid β

The concept that Aβ itself can induce a local inflammatory-type response received impetus from the *in vitro* findings that fibrillar Aβ can bind the complement factor C1 and hence potentially activate the classical complement pathway in an antibody-independent fashion (Rogers et al., 1992). Such activated early complement factors could play an important role in the local recruitment and activation of microglial cells expressing the complement receptors CR3 and CR4 (Rozemuller et al., 1989b). *In vitro* studies indicate that a certain degree of Aβ fibrillization is required for the initiation of the complement system (Snyder et al., 1994). This *in vitro* finding is consistent with the immunohistochemical data in AD brains showing weak or absent immunostaining for early complement components in diffuse plaques composed of non- or low-grade fibrillar Aβ (Eikelenboom and Veerhuis, 1996). The diffuse plaques are not associated with activated microglia and altered neurites, in contrast to the so-called classical and neuritic plaques, which are characterized by congophilic fibrillar Aβ deposits. So, the chronic inflammatory response in AD brains is seen in the plaque containing fibrillar Aβ deposits but not in the diffuse plaque with the non-congophilic low-fibrillar Aβ depositions (Itagaki et al., 1989; Rozemuller et al., 1989a). A wealth of data now implicate the extracellular deposition of Aβ in AD brains as one of the triggers of inflammation. For example, Aβ activates microglia by binding to the receptor for advanced glycation end products (RAGE) (Yan et al., 1998) and to other scavenger receptors (Paresce et al., 1996) Furthermore, the LPS receptor, CD14, interacts with fibrillar Aβ (Fassbender et al., 2003) and microglia kill $A\beta_{1-42}$ damaged neurons by a CD14 dependent process (Bate et al., 2004). The involvement of CD14 in Aβ

induced microglia activation strongly suggests that innate immunity is linked with AD pathology.

3.2. Chromogranin A

Chromogranin A (CGA) represents a secretory 48–53 kDa glycoprotein which is stored and released by neurons in brain regions relevant for several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Of note, neuritic plaques intensely stain for CGA in Alzheimer's disease (Rangon et al., 2003). Experiments showing that exposure of primary rat microglia to CGA resulted in rapid microglial activation characterized by profound morphological changes from an arborized to an amoeboid phenotype lead to the hypothesis that CGA may act as an important stimulator of neuroinflammation (Taupenot et al., 1996). Microglial activation was accompanied by *de novo* synthesis of iNOS and subsequent production of NO (Taupenot et al., 1996). Importantly, CGA was equally or more effective in stimulating iNOS derived NO release relative to microglial stimulation with bacterial lipopolysaccharide. Activation of microglial cells with CGA caused neuronal cell death, however, a direct link between NO or tumor necrosis factor α (TNFα) release and neurodegeneration has not been found in this model (Ciesielski-Treska et al., 1998a,b).

4. Cellular components of neuroinflammation in Alzheimer's disease

Microglia cells represent the brain innate immune system and hence the first line of defense when challenged by bacterial, viral or fungal infection. Although these functions are of major importance and beneficial, it has become clear that microglial activation may also be evoked by endogenous proteins and can significantly contribute to neuronal damage. Along with microglia, astrocytes and even neurons are directly reacting and contributing to the chronic neuroinflammatory changes in AD.

4.1. Microglia

Microglia cells constitute around 10% of all cells in the nervous system. They represent the first line of defense against invading pathogens and serve as specialized sensors for brain tissue injury (Conde and Streit, 2006; Streit et al., 2005). Under pathological situations, such as neurodegenerative disease, stroke, traumatic injury and tumor invasion, these cells become activated, migrate to and surround damaged or dead cells, and subsequently clear cellular debris from the area, similar to the phagocytic active macrophages of the peripheral immune system (Fetler and Amigorena, 2005). Activated microglia up-regulate a variety of surface receptors, including the major histocompatibility complex and complement receptors (Liu and Hong, 2003). They also undergo dramatic morphological changes from a resting ramified phenotype to motile activated amoeboid cells (Kreutzberg, 1996). Once immunostimulated in response to neurodegenerative events, these microglia cells release a variety of proinflammatory mediators including cytokines, reactive oxygen species, complement factors, neurotoxic secretory products, free radical species and NO, all of which can contribute to neuronal dysfunction and cell death, ultimately creating a vicious cycle (Griffin et al., 1998).

Several amyloid peptides and APP can act as potent glial activators (Barger and Harmon, 1997; Dickson et al., 1993; Schubert et al., 2000), and disruption of the APP gene and its proteolytic products delay and decrease microglial activation (DeGiorgio et al., 2002). Microglial cells have been suggested to be preferentially associated with certain amyloid plaque types indicating that plaque development and the degree of microglial reaction are interrelated (D'Andrea et al., 2004). Aβ stimulates a nuclear factor kappa B (NFκB)-dependent pathway that is required for cytokine gene transcription (Combs et al., 2001), activated microglia and reactive astrocytes. Not only Aβ, but also the carboxy-terminal 100 amino acids of APP (CT100), which is also present in senile plaques, can induce astrocytosis and neuronal death. CT100 exposure results in activation of the mitogen-activated protein kinase (MAPK) pathways as well as NFκB (Bach et al., 2001). Additionally, other proteins involved in APP processing have been implicated in the inflammatory response. Loss of presenilin function in presenilin conditional knockout mice leads to differential up-regulation of inflammatory markers in the cerebral cortex, such as strong microglial activation and elevated levels of glial fibrillary acidic protein, complement component C1q, and cathepsin S (Beglopoulos et al., 2004). However, this effect may be unrelated to APP processing, since presenilin is also involved in a variety of other metabolic pathways including the β-catenin pathway and the cleavage of other type I transmembrane proteins, such as Notch, CD44, E-cadherin, ErbB-4, and the Notch ligands (Brunkan and Goate, 2005).

It should be noted that some aspects of microglia function may be beneficial, since activated microglia are able to reduce Aβ accumulation by increasing its phagocytosis, clearance and degradation (Frautschy et al., 1998; Qiu et al., 1998; Yan et al., 2003). Thus, secreted $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides are constitutively degraded by the insulin degrading enzyme (IDE), a metalloprotease released by microglia and neural cells. Finally, microglia can also secrete several trophic factors, such as the glia-derived neurotrophic factor (GDNF), which exert a well documented neuroprotective function (Liu and Hong, 2003).

4.2. Astrocytes

Astrocytes participate in β-amyloid clearance and degradation, provide trophic support to neurons, and form

a protective barrier between Aβ deposits and neurons (Wyss-Coray et al., 2003; Koistinaho et al., 2004). The presence of large numbers of astrocytes associated with Aβ deposits in AD suggests that these lesions generate chemotactic molecules that mediate astrocyte recruitment. It has been shown that astrocytes throughout the entorhinal cortex of AD patients gradually accumulate $A\beta_{1-42}$ positive material, and the amount of this material correlates positively with the extent of local AD pathology. $A\beta_{1-42}$ within these astrocytes appears to be of neuronal origin, possibly accumulated by phagocytosis of locally degenerated dendrites and synapses, especially in the cortical molecular layer (Nagele et al., 2003). In support of this finding, recent evidence suggests that astroglial cells are able to phagocytize Aβ peptides, a process which may depend on their apolipoprotein E (ApoE) status, suggesting that ApoE polymorphisms may influence the risk to develop AD by affecting astroglial Aβ phagocytosis (Jiang et al., 1998; Niino et al., 2001). In contrast, a recent report suggests that astrocytes could also act as a source for Aβ because they overexpress BACE1 in response to chronic stress (Rossner et al., 2005). While it remains unclear to which degree astrocyte activation contributes to Aβ generation or its clearance, it seems apparent that astrocytes contribute to inflammation. For example, astrocytes have been shown to express iNOS and the L-arginine-supplying enzyme argininosuccinate synthetase and consequently contribute to NO-mediated neurotoxicity (Heneka et al., 2001; Heneka and Feinstein, 2001). Although astrocytes serve as a constant and important source of neurotrophic factors under physiological conditions, *in vitro* and *in vivo* experiments suggest that chronically activated inflammatory astrocytes may not generate significant amounts of these molecules (Nagatsu and Sawada, 2005).

Although it is generally accepted that Aβ deposition is a potent glial activator, astrocyte and microglial activation could be an early event in the disease, occurring even in the absence of focal Aβ deposition (Nunomura et al., 2001). In support of this hypothesis, a clinical study detected microglial activation at very early stages of AD, comparing PET and volumetric magnetic resonance imaging of the brain in patients with mild to moderate dementia to healthy individuals (Cagnin et al., 2001). In parallel, it has been recently reported that focal glial activation preceeds amyloid plaque deposition in APPV717I transgenic mice at 3 month of age (Heneka et al., 2005a). Because these animals show both cognitive deficits and focal glial cytokine production well before Aβ plaque deposition (Moechars et al., 1999), it seems likely that senile plaques are, at least at the beginning of the disease, not the cause of glial activation, but rather a response to Aβ oligomers or protofibrils (Hu et al., 1998; Lindberg et al., 2005; White et al., 2005). Interestingly, young APPV717I transgenic mice show a significant decrease of hippocampal long-term potentiation (LTP), a mechanism essential for memory storage and consolidation. Because cytokines such as TNF-α, interleukin-1β (IL-1β) and interleukin 6 (IL-6) directly impair neuronal function and suppress hippocampal LTP (Tancredi et al., 1992; Murray and Lynch, 1998) early focal inflammatory events may contribute to neuronal dysfunction well before neuronal cell death and parenchymal volume reduction become apparent.

4.3. Neurons

While neurons were traditionally believed to be passive bystanders in neuroinflammation, more recent evidence suggests that neurons themselves are capable of producing inflammatory mediators. Thus, neurons can serve as source of complement, COX-2-derived prostanoids (Davis and Laroche, 2003; Pavlov and Tracey, 2005; Rozemuller et al., 1989b; Simard et al., 2006; Natarajan and Bright, 2002; Moore et al., 2005), and several cytokines including IL-1β, IL-6, and TNF-α (Botchkina et al., 1997; Breder et al., 1993; Gong et al., 1998; Murphy et al., 1999; Orzylowska et al., 1999; Suzuki et al., 1999; Tchelingerian et al., 1994; Yan et al., 1995; Hoozemans et al., 2004; Aloisi et al., 1992; Thery et al., 1992; Kim et al., 2001; Szczepanik et al., 2001b; Grammas and Ovase, 2001) and M-CSF (Du et al., 1997). Although COX-2 expression is driven by physiological synaptic activity (Yamagata et al., 1993; Yermakova and O'Banion, 2000), it is possible that neurons themselves may exacerbate local inflammatory reactions and thus contribute to their own destruction in AD. As a further factor, expression of the inflammatory induced enzyme iNOS has been described in degenerating neurons in AD brains (Vodovotz et al., 1996; Lee et al., 1999; Heneka et al., 2001), and compelling evidence exists for iNOS related long-term NO release and NO dependent peroxynitrite formation (Smith et al., 1997). Glial and neuronal derived NO and peroxynitrite have been demonstrated to cause neuronal dysfunction and cell death *in vitro* and *in vivo* (Boje and Arora, 1992; Heneka et al., 1998). Alternatively, some of the classical pro-inflammatory mediators such as TNF-α and low concentrations of NO may actually confer neuroprotection rather than destruction in the brain and therefore constitute a defense mechanism against local inflammatory reactions.

5. Pro- and antiinflammatory mediators

The neuroinflammatory response observed in AD is characterized by a whole array of pro- and antiinflammatory mediators including members of the complement cascade, chemo- and cytokines as well as inflammatory enzyme systems. Several of these factors may promote neurodegenerative mechanisms while others may rather limit ongoing inflammatory changes or even exert beneficial neurotrophic effects. Thus, not a single mediator but rather the entire spectrum of inflammatory agents will determine whether beneficial or detrimental effects prevail.

5.1. Complement

The complement system represents a complex and tightly regulated attack cascade designed to destroy invaders and assist in the phagocytosis of waste materials. The components of this system carry out four major functions: recognition, opsonization, inflammatory stimulation and direct killing through the membrane attack complex (MAC) (McGeer and McGeer, 2002). In addition to triggering the generation of a membranolytic complex, complement proteins interact with cell surface receptors to promote a local inflammatory response that contributes to the protection and healing of the host. Complement activation causes inflammation and cell damage, yet it is essential for eliminating cell debris and potentially toxic protein aggregates (Shen and Meri, 2003).

The complement system consists of some 30 fluid-phase and cell-membrane associated proteins that can be activated by three different routes: the classical pathway (involving C1q, C1r, C1s, C4, C2, and C3 components) is activated primarily by the interaction of C1q with immune complexes (antibody–antigen), but activation can also be achieved after interaction of C1q with non-immune molecules such as DNA, RNA, C-reactive protein, serum amyloid P, bacterial lipopolysaccharides, some fungal and virus membranes, and as already mentioned, fibrillar Aβ. The initiation of the alternative pathway (involving C3, factor B, factor D, and properdin) does not require the presence of immune complexes and leads to the deposition of C3 fragments on target cells. Mannose-binding lectin (MBL), a lectin homologous to C1q, can recognize carbohydrates such as mannose and N-acetylglucosamine on pathogens and initiate the complement pathway independently of both the classical and the alternative activation pathways. Like the C1 complex in the classical pathway, MBL is associated with two serine proteases that cleave C4 and C2 components, leading to the formation of the classical C3 convertase (van Beek et al., 2003).

Various brain cells can produce complement proteins to recognize and kill pathogens locally. Cell lines and primary cultures of human origin were used to show that glial and neuronal cells could produce most complement proteins, particularly after stimulation with inflammatory cytokines (Gasque et al., 1995). Studies using RT-PCR have shown locally upregulated complement mRNA in AD brain, especially in the areas of primary pathology: entorhinal cortex, hippocampus, and midtemporal gyrus (Yasojima et al., 1999b). Numerous groups have reported the association of complement proteins of the classical pathway, particularly the MAC, with amyloid plaques and neurofibrillary tangles in AD brains (Webster et al., 1997).

Studies of mutant mice lacking complement proteins suggest that impaired phagocytosis can result in immune-mediated tissue damage and inflammation (Botto, 1998; Taylor et al., 2000). Wyss-Coray and colleagues demonstrated that complement activation can protect against Aβ-induced toxicity and may reduce the accumulation or promote the clearance of senile plaques (Wyss-Coray et al., 2002). AD mice expressing a soluble form of the complement inhibitor Crry, which blocks C3 activation, under the control of the glial fibrillary acidic protein promoter displayed higher Aβ deposition and more prominent neurodegeneration than age-matched control mice. However, more recently it was reported that transgenic mouse models of AD lacking C1q showed reduced pathology, consisting of decreased numbers of activated glia and improved neuronal integrity, without changes in plaque area. These data suggest that at stages when fibrillar plaque pathology is present, C1q exerts a detrimental effect on neuronal integrity, most likely through the activation of the classical complement cascade and the enhancement of inflammation (Fonseca et al., 2004).

5.2. Chemokines

Recent experiments have focused on understanding the role of chemokines and their receptors in AD neuroinflammation. The chemokine family consists of over 50 different molecules that confer chemotaxis, tissue extravasation, and functional modulation of leukocyte function during inflammation (Luster, 1998; Owens et al., 2005). The importance of chemokine generation in AD brain is underscored by the fact that these molecules may potently regulate microglial migration and recruitment of astrocytes to the area of neuroinflammation, and thus are responsible for the extent of local inflammation. In addition, recent studies using chimeric mice grafted with green fluorescent protein expressing bone marrow, indicate that many of the so-called microglia represent invading macrophages from peripheral blood (Stalder et al., 2005; Simard et al., 2006) suggesting a chemotactic stimulus from the brain. Whether this also occurs in human AD is yet to be determined. The CXC subclass of chemokines is considered one of the two major chemokine subfamilies and its members (e.g. IL-8) are primarily chemotactic for neutrophils and endothelial cells. The conserved glutamate–leucine–arginine (ELR) motif within the receptor-binding domain of these proteins (Strieter et al., 1995) distinguishes them from non-ELR CXC chemokines such as IP-10, which primarily attract activated T cells (Strieter et al., 1995). The CC chemokine subfamily, whose members include MIP-1α, MCP-1, and RANTES, do not affect neutrophils but are chemotactic for monocytes/macrophages, T lymphocytes, basophils and eosinophils. Seven transmembrane, G-protein-coupled cell-surface receptors mediate the biological activities of chemokines and these receptors are named according to their chemokine subfamily classification. At present there are five known CXC receptors (CXCR1 to CXCR5) and nine CC receptors (CCR1 to CCR9) (Charo and Ransohoff, 2006).

While it has been reported that chemokines exert physiological action in healthy brain (Hesselgesser and

Horuk, 1999), the majority of studies have focused on the expression pattern of chemokines and their respective receptors in neurological diseases such as multiple sclerosis, traumatic brain injury and stroke. All of these disorders share disruption of the blood brain barrier as an important pathogenetic event subsequently allowing peripherial leukocytes to infiltrate the lesion site (Glabinski and Ransohoff, 1999). In contrast, no convincing evidence exists for blood brain barrier disruption or significant leukocyte infiltration in the AD brain. However, several chemokines and chemokine receptors have been found to be upregulated in the AD brain (Xia and Hyman, 1999), and chemokines may play an important role for recruiting microglia and astroglia to sites of Aβ deposition. Thus, Aβ stimulated human monocytes generate IL-8, MCP-1, MIP-1α and MIP-1β *in vitro* (Smits et al., 2002), and microglia cultured from rapid autopsies of AD and non-demented patients reveal an increased expression of IL-8, MCP-1 and MIP-1α after experimental exposure to Aβ (Lue et al., 2001a). Neuropathological studies have found MCP-1 (Ishizuka et al., 1997) and increased expression of CCR3 and CCR5 in reactive microglia (Xia et al., 1998). Supporting the hypothesis that astrocytes actively contribute to the inflammatory disease component, MIP-1β has been detected in reactive astrocytes nearby Aβ plaques (Xia et al., 1998).

6. Inflammatory cytokines

The cytokine class of inflammatory mediators is secreted by microglia and astrocytes surrounding β-amyloid neuritic plaques. Cytokines associated with AD include several interleukins (ILs), TNF-α and TGFβ along with several others. Their production is increased in inflammatory states and they function by regulating the intensity and duration of the immune response (Tuppo and Arias, 2005).

In astrocytes, IL-1 induces IL-6 production, stimulates iNOS activity (Rossi and Bianchini, 1996), and induces the production of M-CSF (Frei et al., 1992; Aloisi et al., 1992; Thery et al., 1992). In addition, IL-1 enhances neuronal acetylcholinesterase activity, microglial activation and additional IL-1 production, with consequent astrocyte activation, and expression of the cytokine S100β by astrocytes, thereby establishing a self propagating cycle (Griffin et al., 1998; Mrak and Griffin, 2001). IL-6 promotes astrogliosis (Selmaj et al., 1990), activates microglia (Heyser et al., 1997), and stimulates the production of acute phase proteins (Castell et al., 1989). IL-6 knockout mice exhibit a facilitation of radial maze learning over 30 days and show a faster acquisition, suggesting a possible involvement of IL-6 in memory processes (Braida et al., 2004). TNF-α has both pro-apoptotic and anti-apoptotic effects. This proinflammatory cytokine accounts for most of the neurotoxic activity secreted by monocytes and microglia (Combs et al., 2001). On the other hand, TNF-α has been reported to have neuroprotective properties (Akiyama et al., 2000) in the AD brain.

In addition to the general role of cytokines, AD-specific interactions of certain cytokines and chemokines with Aβ may be pathophysiologically relevant. For example, IL-1 can regulate APP processing and Aβ production *in vitro* (Blasko et al., 1999). In turn, fibrillar Aβ has been reported to increase neurotoxic secretory products, proinflammatory cytokines and reactive oxygen species (Eikelenboom et al., 1994; McGeer and McGeer, 1995; Eikelenboom and van Gool, 2004). Cultured rat cortical glia exhibit elevated IL-6 mRNA after exposure to the carboxy-terminal 105 amino acids of APP (Chong, 1997). IL-1, IL-6, TNF-α MIP-1α and MCP-1 increase in a dose-dependent manner after cultured microglia are incubated with Aβ (Floden and Combs, 2006; Lindberg et al., 2005; Benveniste et al., 2001; Butovsky et al., 2005; Veerhuis et al., 2005; Hanisch, 2002; Lue et al., 2001b; Lee et al., 2002). Production of IL-6 and M-CSF by human neurons is reportedly stimulated by glycation endproduct-modified tau and Aβ (Akiyama et al., 2000). Additionally, Aβ is able to stimulate a NFκB-dependent pathway that is required for cytokine production (Combs et al., 2001). The production of interleukins and other cytokines and chemokines may also lead to microglial activation, astrogliosis, and further secretion of proinflammatory molecules and amyloid, thus perpetuating the cascade (Ho et al., 2005).

A second general category of cytokine action is manifested by inhibitory, anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1Ra), IL-4, IL-10 and TGF-β. Some of these are reportedly elevated in AD, consistent with induction of homeostatic mechanisms in neuroinflammation (Grammas and Ovase, 2001; Rota et al., 2006; Szczepanik et al., 2001a). The use of anti-inflammatory cytokines such as IL-4 and TGF-β could be beneficial, because they are able to inhibit CD40 and class II MHC by restricting their expression and activity (Benveniste et al., 2001). However, overexpression of TGFβ in transgenic mice leads to changes in the microvasculature, including age-related amyloid deposition (Wyss-Coray et al., 2000), reflecting the multi-functional nature of many cytokines.

Whereas transgenic mouse models are widely used to study *in vivo* consequences of APP processing, only a limited number of studies has characterized neuroinflammatory changes in these animals. All but one study used APP695 transgenic mice (Tg2576), and results were controversial. Mehlhorn and colleagues analyzed APP695 transgenic animals from 2 to 14 months of age but failed to detect mRNA levels of several cytokines including IL-1-α/β, IL-6, IL-10, IL-12 and IFN-γ using a ribonuclease protection assay (Mehlhorn et al., 2000). In the same study, IL-1-β-positive astrocytes were detected in close proximity to Aβ deposition, whereas immunohistochemistry for TNF-α, IL-1-α, IL-6, and MCP-1 was negative. In contrast, Sly and colleagues detected TNF-α mRNA as early as 6 months of age (Sly et al., 2001), and Abbas and colleagues detected IFN-γ and IL-12 mRNA and protein levels by *in situ* hybridization and immunohistochemistry in 9-month-old

APP 695 transgenic mice (Abbas et al., 2002. Moreover, IL-1-β, TNF-α and IL-10 were found by immunohistochemistry in 12- to 13-month-old animals (Benzing et al., 1999; Apelt and Schliebs, 2001). The variability of findings in the same transgenic mouse line is likely caused by different techniques employed and indicates the difficulty of assessing inflammatory changes in these animal models. In contrast to animal models, nearly all cytokines that have been studied in AD, including IL-1α/β, IL-6, TNF-α, IL-8, and TGF-β, seem to be upregulated in AD compared to control individuals (Akiyama et al., 2000; Tuppo and Arias, 2005).

In addition to these primarily immunohistological evaluations, an association of AD with several polymorphisms of proinflammatory genes has been described, including IL-1 (Nicoll et al., 2000), IL-6 (Papassotiropoulos et al., 1999), TNF-α (McCusker et al., 2001; Perry et al., 2001), and α1-antichymotrypsin, an acute phase protein (Kamboh et al., 1995). However, none of the various members of the interleukin cytokine family that are associated with AD actually map to chromosomal regions with evidence of genetic linkage (Tanzi and Bertram, 2005). Thus, although inflammation and the upregulation of inflammatory mediators like the interleukins are regularly observed in AD brain, it appears less likely that variation at the genomic level of these proteins makes a large contribution to AD risk in general.

6.1. Cyclooxygenase and prostanoids

The two isoforms of cyclooxygenases, the mainly constitutively expressed COX-1 and the inducible COX-2, catalyze key steps of prostanoid synthesis in mammalian cells (O'Banion, 1999). Downstream of both COX-1 and COX-2, several other enzymes regulate the generation of a whole spectrum of prostanoids, some of which may be neuroprotective and others neurotoxic. Thus, the composition and proportion of all prostanoids together may actually determine whether the activity of COX enzymes is beneficial or detrimental.

In vitro, LPS activated microglial cells and IL-1β-stimulated astroglial cells are capable of synthesizing COX-2 (Bauer et al., 1997; O'Banion et al., 1996). In contrast to peripheral monocytes, cultured rat microglia cells do not synthesize COX-2 in response to IL-1 or IL-6 (Bauer et al., 1997), suggesting that COX-2 regulation differs between CNS and peripheral cells. In rat microglial cell cultures, the major enzymatic product of COX-2 appears to be prostaglandin E_2 (PGE_2). Because PGE_2 itself is able to induce COX-2 in microglial cells (Minghetti et al., 1997), an autocrine or paracrine amplification of COX-2 in microglial cells and perhaps other cell types cells is possible. PGE2 acts on four different receptors: EP1–EP4 (Narumiya et al., 1999). EP1 and EP2 receptors have been detected in cultured microglia, while EP3 receptors are also present in activated microglia *in vivo* (Slawik et al., 2004). Microglial EP2 receptors inhibit phagocytosis and enhance neurotoxic activities of microglia (Shie et al., 2005a,b). In cultured rat and human astrocytes, EP2 and EP4 receptors are present and may potentiate glial cytokine production (Fiebich et al., 2001). PGE2 may also act on the neuronal EP2 receptor, which is involved in apoptosis, although investigations of the role of neuronal EP2 activation on neuronal cell death have yielded conflicting results and suggest a neuroprotective role of neuronal EP2 stimulation under several pathophysiological circumstances (Bilak et al., 2004; Lee et al., 2004; McCullough et al., 2004; Takadera et al., 2004). Indeed, deletion of EP2 in a double transgenic AD mouse model led to decreased oxidative stress and amyloid burden (Liang et al., 2005). In conclusion, neuronal and glial secretion of PGE_2 may impair phagocytotic clearance of Aβ by binding to the microglia EP2 receptor and enhancing microglial toxicity. However the role of PGE2 in neurodegeneration may be far more complex due to the presence of other EP receptor subtypes on microglial cells and the effects of PGE_2 on other cell types. Neuronal death elicited by excitotoxins is elevated in transgenic animals with high expression of COX-2, suggesting that COX-2 expression may further interact with other pathogenetic mechanisms (Kelley et al., 1999).

COX-2 is upregulated in many inflammatory disorders (Dubois et al., 1998). However data about COX-2 expression in AD brain is conflicting. Several investigators have detected increased levels of COX-2 mRNA and protein staining in AD tissue (Ho et al., 2001; Kitamura et al., 1999; Oka and Takashima, 1997; Yasojima et al., 1999a) while others have found decreased COX-2 expression, particularly in late stage AD (O'Banion et al., 1997; Yermakova and O'Banion, 2001; Hoozemans et al., 2004). In addition to differences in tissue sources and methodologies employed, a well-controlled post mortem study indicated a higher variability of COX-2 mRNA in the brains of AD patients compared to age matched controls (Lukiw and Bazan, 1997). Furthermore, COX-2 expression is not restricted to microglial or astroglial cells in AD brain; indeed it is predominantly observed in neurons of AD brains and age matched controls (O'Banion et al., 1997; Yermakova and O'Banion, 2001).

Interestingly, COX-1 is prominently expressed by microglia in rodent and human brain (Yermakova et al., 1999; Hoozemans et al., 2001) and appears to be modestly elevated in AD brain (Yermakova et al., 1999). Whether microglial COX-1 contributes to neuroinflammation in AD has not been established; however, COX-1 activity has been linked to PGE_2 production in several experimental models of acute brain injury (Candelario-Jalil et al., 2003; Moore et al., 2005).

6.2. NO synthase, nitric oxide and free radicals

NO is a gaseous free radical, which is generated through the conversion of L-arginine to L-citrulline by enzymes of the nitric oxide synthase family (Bredt and Snyder, 1990). Ca^{2+}/calmodulin-dependent constitutive isoforms are present in

neuronal and endothelial cells, and produce NO in a highly regulated manner. iNOS is rapidly expressed in macrophages, microglia and astrocytes upon stimulation with lipopolysaccharide (LPS) or several cytokines (Corradin et al., 1993; Galea et al., 1992; Simmons and Murphy, 1992; Stuehr and Marletta, 1985). This isoform produces large amounts of NO in a Ca^{2+}-independent manner for prolonged periods of time. NO generated by iNOS is cytotoxic for invading microorganisms and tumor cells (Moncada et al., 1992). However, induction of iNOS may also have deleterious consequences for the host since vasodilatation, organ dysfunction and septic shock are partly mediated by an overproduction of NO (Thiemermann, 1994). The consequences of iNOS induction in glial cells, however, seem to depend on a variety of factors including the type of cell cultures used. Both deleterious effects on neurons and unaffected neuronal viability after iNOS induction in mixed glial–neuronal cultures have been reported (Chao et al., 1996; Dawson et al., 1994; Demerle-Pallardy et al., 1993; Skaper et al., 1995). Importantly, iNOS expression and NO generation have been described in several brain pathologies including demyelinating diseases (Willenborg et al., 1999a, b), cerebral ischemia (del Zoppo et al., 2000), AIDS dementia (Hori et al., 1999), amyotrophic lateral sclerosis (Almer et al., 1999), and AD (Wallace et al., 1997; Weldon et al., 1998; Heneka et al., 2001; Lee et al., 1999).

In addition to glial iNOS, neuronal iNOS may impact neurological disorders. For example, Vodovotz and colleagues (Vodovotz et al., 1996) reported that NFT-bearing neurons in affected brain regions of patients suffering from AD express iNOS. Further support for a role for iNOS in the inflammatory pathomechanisms involved in AD, is provided by reports of increased nitrotyrosine staining in AD brains, indicating sustained exposure and oxidative damage by peroxynitrite, an intermediate NO reaction product (Smith et al., 1997). In addition to NFTs and SPs, eosinophilic rod-like inclusions (Hirano bodies) are observed in AD brains and iNOS-immunoreactivity has been detected in association with Hirano bodies in the pyramidal layer of the CA1 region of the hippocampus and to a lesser extent in the stratum lacunosum (Lee et al., 1999). In that study, control brains showed only occasional iNOS-positive staining associated with rare Hirano bodies, while other studies, as well as our own experiments, failed to detect iNOS in control brains (MTH, unpublished observations).

To further characterize the pathway involved in neuronal iNOS expression in AD, we investigated expression of the enzyme argininosuccinate synthetase (AS) and its possible colocalization with iNOS in AD brain (Heneka et al., 2001). AS is the rate limiting enzyme in the metabolic pathway that recycles the iNOS substrate L-arginine from its catalytic byproduct L-citrulline. Several brain areas of AD patients showed a marked increase in AS expression in neurons and GFAP-positive astrocytes. Occasionally, AS expression was also detected in CD 68-positive activated microglia cells. Expression of AS was colocalized with iNOS immunoreactivity in neurons and glia. These results suggest that neurons and glial cells in AD not only express iNOS, but also AS. Because an adequate supply of L-arginine is indispensable for long-term NO generation by iNOS, coinduction of AS could enable cells to sustain NO generation, which could subsequently damage the iNOS expressing neurons as well as surrounding tissue.

7. Inflammation-permissive factors in AD

Occurrence and deposition of aggregated, misfolded or phosphorylated proteins may play the pivotal role for the induction and ongoing stimulation of inflammation in the AD brain. However, since some of these proteins may well occur in the normal aging brain without evoking such a dramatic immune response, it may be hypothesized that several other changes in AD are facilitating inflammation. Loss of aminergic brains stem nuclei, such as the locus ceruleus and the nucleus basalis of Meynert, may result in an impaired control of neuroinflammation in the AD brain.

7.1. Locus ceruleus cell death

The locus ceruleus (LC) is located in the pontine tegmentum and serves as the main subcortical site for the synthesis of noradrenaline (NA) (Freedman et al., 1975). Ascending noradrenergic axons of the dorsal portion of the LC preferentially project to the hippocampus, the frontal and entorhinal cortex and to a minor extent to various other brain regions. Neuronal cell death of aminergic brain stem nuclei such as the LC and the dorsal raphe nucleus is a well defined, very early feature of AD that was first described by Forno (Forno, 1966) and later confirmed by several groups (Mann et al., 1980, 1982; Wilcock et al., 1988). In AD, the central and dorsal portion of the LC show the most extensive loss of cells (Marcyniuk et al., 1986). LC loss and the subsequent degeneration of ascending noradrenergic axons lead to decreased NA levels in the LC projection areas (Adolfsson et al., 1979; Iversen et al., 1983) whereas adrenergic receptors are upregulated in response to noradrenergic deafferentiation (Kalaria et al., 1989).

Besides its role as a classical neurotransmitter, NA acts as a potent suppressor of inflammatory gene transcription within the brain (Marien et al., 2004; Feinstein et al., 2002b). LC loss and subsequently decreasing NA levels may therefore be permissive for inflammatory mechanisms, which are otherwise controlled by physiologically released NA. Specifically, NA has been shown to suppress the generation and secretion of several inflammatory molecules including microglial synthesis of TNF-α and astrocytic expression of class II antigens. Studies from ourselves and others show that NA can also inhibit LPS- and cytokine-dependent iNOS expression in astrocytes and microglial cells, mediated by the activation of β-adrenergic receptors, and increases in cAMP (Gavrilyuk et al., 2002).

Since the initial neuropathological description, a number of studies have also demonstrated significant correlation of LC cell death or decreased cortical NA levels with severity and duration of dementia in AD (Bondareff et al., 1987; German et al., 1992; Yates et al., 1983). Interestingly, LC loss correlates better with the clinical course of the disease and the severity of dementia than loss of the nucleus basalis of Meynert and perturbation of the cholinergic system (Zarow et al., 2003). It has been argued that LC degeneration may occur as a consequence of primary degenerative changes in the cortical projection areas. However, even aged APP transgenic mice that do show an intense Aβ plaque load do not reveal any significant reduction of LC cell numbers or cortical NA levels, suggesting that LC cell death occurs independently of Aβ deposition and not in response to neurodegenerative events in its projection areas. This assumption is further supported by a recent finding that shows significant LC degeneration even in patients suffering from mild cognitive impairment, a clinical phase widely regarded as a prestage of AD (Grudzien et al., in press).

Experimentally induced noradrenergic depletion can be achieved by systemic treatment of animals with the selective noradrenergic neurotoxin *N*-(2-chloroethyl-*N*-ethyl-2 bromobenzylamine (DSP4 (Fritschy and Grzanna, 1989). DSP4 causes widespread degeneration of LC axon terminals, decreased activity, and loss of LC neurons (Fritschy and Grzanna, 1989; Olpe et al., 1983). Moreover DSP4 also impairs electophysiological functions of remaining LC neurons (Magnuson et al., 1993) and NA depletion by DSP4 has been demonstrated to markedly increase neurodegeneration induced by N-metyhl-4 phenyl 1,2,3,6-tetrahydropyridine (Mavridis et al., 1991) and cerebral ischemia (Nishino et al., 1991).

Using a similar model we showed that DSP4 treatment of rats caused degeneration of noradrenergic projections and cell death of LC neurons, but did not affect substantia nigra neuron survival. Local application of Aβ into the rat cortex resulted in a greater and prolonged IL-1β expression in microglial cells in noradrenergic depleted animals as compared to controls with an intact NA system. Likewise expression levels of IL-6, iNOS and COX-2 were significantly increased in NA depleted cortices. Interestingly, iNOS expression was completely restricted to microglial cells in controls, whereas NA depleted animals showed widespread iNOS expression in pyramidal neurons (Heneka et al., 2002, 2003), a phenomenon previously reported in AD brains (Vodovotz et al., 1996; Lee et al., 1992; Heneka et al., 2001). Noradrenergic depletion in APP transgenic mice led to a similar picture, with increased glial activation and amyloid deposition, as well as evidence of increased neurodegeneration (Heneka et al., 2006). Additional *in vitro* experiments assessing microglial migration and phagocytosis found that NA, while suppressing inflammatory gene transcription, increased microglial migration and phagocytic capacity at the same time. This may indicate that NA serves as an important factor that switches activated microglial cells from a cytokine releasing phenotype to a more mobile and phagocyting one. In summary, LC loss and noradrenergic depletion of cortical and hippocampal areas may promote neuropathological and inflammatory changes in a vicious, sustained cycle in AD.

7.2. Basal forebrain cell death

Similar to cell death observed in the locus ceruleus, the basal forebrain nucleus (Ncl. basalis of Meynert) degenerates in AD. The neuronal loss observed here is thought to be the major factor for the subsequent decrease of acetylcholine (ACh) in the cortical projection regions of its neurons. The hypothesis that the loss of ACh is permissive for neuroinflammatory events in cortical projection areas was suggested by finding that efferent stimulation of the vagus nerve decreases the release of TNF-α and various other proinflammatory mediators by macrophages of the gastrointestinal tract (Borovikova et al., 2000; Wang et al., 2003; Pavlov and Tracey, 2005). This effect has been attributed to the presence of the α7 subunit of the ACh receptor. Interestingly, glial cells of the CNS such as astrocytes and microglia cells express the α7 subunit (Graham et al., 2003) and expression of the α7 subunit is increased in astrocytes derived from AD patients compared to age-matched controls (Teaktong et al., 2003).

7.3. Diabetes mellitus

Diabetes mellitus (DM) is characterized by either an impaired production of insulin due to primary islet cell death or by insulin resistance of normally insulin responsive cells. The latter form is often observed at later stages of life and termed non-insulin-dependent DM (NIDDM), because most of these patients can achieve control over the blood glucose level without subcutaneous insulin administration. NIDDM often becomes apparent at a similar time as AD and is an established risk factor for the development of AD (Ristow, 2004). While the connecting and underlying mechanisms are yet unclear, one may hypothesize that impaired immunological defenses of NIDDM patients and frequent peripherial infections contribute to the course of AD. Specifically, frequent infections result in higher levels of circulating cytokines and bacterial cell wall components such as lipopolysaccharides. Animal experiments suggest that the peripherial administration of lipopolysaccharides can contribute and enhance existing brain inflammation especially within the hippocampus (Semmler et al., 2005), and ultimately lead to an increased rate of Aβ plaque deposition (Sheng et al., 2003). In addition, recent work by Fishel et al. demonstrated that mild hyperinsulinemia in humans provoked an increase in cytokines and prostanoids in the CSF, suggesting stimulation of inflammatory brain circuits in NIDDM (Fishel et al., 2005).

8. Cytokine driven feedback mechanisms

Apart from self-propagation and direct cytopathic effect on neurons, cytokines may more directly contribute to AD related neurodegeneration. Thus, studies performed in transgenic animals suggest that cerebral amyloid deposition is increased under inflammatory conditions (Games et al., 1995; Guo et al., 2002). Moreover, these animals do not develop amyloid plaques unless inflammation is induced suggesting that inflammatory molecules either raise the susceptibility for Aβ deposition and aggregation or directly influence the APP processing pathway.

Several lines of evidence suggest that cytokines may promote Aβ formation, aggregation and deposition at multiple levels. For example, IL-1 has been implicated in the transformation of diffuse β-amyloid aggregates into β-amyloid plaques (Akiyama et al., 2000). Furthermore, adding the amyloid plaque associated proteins α1-antichymotrypsin (ACT) or apolipoprotein E to preparations of synthetic Aβ peptide *in vitro*, increased polymerization of Aβ into amyloid filaments was observed (Ma et al., 1994). In addition, cytokines are able to transcriptionally upregulate BACE1 mRNA, protein and enzymatic activity (Sastre et al., 2003). BACE1 and presenilin-1 are key enzymes for Aβ formation since in their absence, Aβ synthesis is either abolished or considerably reduced (Walter et al., 2001). These results are in line with data concerning increased expression and activity of BACE1 in NT2 neurons exposed to oxidative stress (Tamagno et al., 2002), in experimental traumatic brain injury (Blasko et al., 2004), and in reactive astrocytes in chronic models of gliosis (Hartlage-Rubsamen et al., 2003). Prolonged cytokine treatment can also influence βAPP maturation and secretion (Blasko et al., 1999, 2000). Finally, cytokines have been shown to increase APP expression. For example, TGF-β treatment of human astrocytes markedly elevated APP mRNA levels, and also increased the half-life of APP message by at least five-fold (Amara et al., 1999). In addition, IL-1α and IL-1β increased APP synthesis by up to 6-fold in primary human astrocytes and by 15-fold in human astrocytoma cells without changing the steady-state levels of APP mRNA (Rogers et al., 1999).

Cytokines may also be involved in neurofibrillary tangle formation since chronic IL-1β release from implanted capsules led to phosphorylation of neurofilaments and increased phospho-tau immunoreactivity in the rat hippocampus (Sheng et al., 2000). Similar studies have been reported in cultures of cortical neurons (Li et al., 2003). The possibility that IL-1 represents a link between Aβ formation, microglial activation and tau phosphorylation was recently supported by work in a triple transgenic mouse model of AD. In these animals, tau phosphorylation appears to proceed amyloid deposition (Oddo et al., 2003, 2006). However, phosphorylated tau epitopes were observed in young animals that were chronically treated with intraperitoneal LPS prior to the time that plaques appear (Kitazawa et al., 2005). These changes in tau were associated with increased levels of IL-1β and appeared to result from activation of cdk5 kinase (Kitazawa et al., 2005).

9. Functional and structural consequences of neuroinflammation in AD

Over the past decade, numerous lines of evidence have strongly suggested that neuroinflammation contributes to AD pathogenesis. Irregardless at which time point of the disease it occurs, it seems clear that once initiated, inflammatory pathomechanisms can affect the AD brain. Functional and structural consequences may be differentiated to understand the various levels at which inflammation may contribute to AD.

9.1. Inflammation triggered functional impairment

LTP represents a key function of memory formation and consolidation. Since several cytokines including TNF-α, IL-1β and IFN-γ are able to suppress hippocampal LTP, the presence of these inflammatory molecules alone may be sufficient to induce neuronal dysfunction without structurally affecting neurons (Tancredi et al., 1992, 2000; Murray and Lynch, 1998). Similar to cytokines, immunostimulated and iNOS derived NO also impairs LTP (Wang et al., 2004; Mori et al., 2001). Since iNOS expression is a long-lasting event, surrounding neurons face a sustained production of high NO concentrations. Functional impairment by increased cytokine and nitric oxide production may be of special relevance for the early stages of AD, when patients present with mild cognitive decline, often at a time when brain MRI scans fail to detect any atrophy of cortical or limbic structures.

9.2. Structural damage

In addition to neuronal dysfunction, several inflammation-evoked molecules may directly exert cytotoxic effects on neurons as already described. Despite descriptions of paradoxical protective effects for some of these mediators such as C5a (Osaka et al., 1999; Pasinetti et al., 1996; Tocco et al., 1997) or TNF-α (Barger and Harmon, 1997; Barger et al., 1995; Feuerstein et al., 1994), the majority of experiments suggest that cytokines contribute to neuronal cell death. Further support for a more cytopathic role of these molecules comes from transgenic animal experiments showing that mice expressing these inflammatory proteins under brain-specific promoters invariably exhibit profound pathologic changes (Probert et al., 1995; Stalder et al., 1998; Wyss-Coray et al., 1995, 1997).

In addition to cytokine and complement generation, microglia and astrocytes may contribute by other means to neurodegeneration: While resting glial serve as an important source of various trophic factors such as GDNF, BDNF and others, chronic inflammatory activation may decrease the generation and release of these factors. It has therefore been

suggested that inflammatory activation also leads to a significant trophic factor withdrawal which further contributes to neurodegeneration (Nagatsu and Sawada, 2005).

Excitotoxic mechanisms significantly contribute to the neuronal loss in AD (Barger et al., 1993; Hensley et al., 1994; Smithswintosky et al., 1994). It is important to note, that the cytotoxic effects of iNOS derived NO and several proinflammatory molecules are not simply additive but potentiate NMDA or kainate induced excitotoxicity (Hewett et al., 1994; Morimoto et al., 2002).

10. Antiinflammatory treatment strategies

Neuroinflammatory changes may even occur at early stages in the AD brain and significantly contribute to the pathogenesis of the disease. This raises the question whether therapeutic strategies can be developed which successfully target the ongoing inflammation.

10.1. NSAIDs as preventive treatment for AD

Epidemiological studies have convincingly documented a beneficial effect of non-steroidal anti-inflammatory drugs (NSAIDs) in AD (Rogers et al., 1993; McGeer et al., 1996; Anthony et al., 2000; Breitner, 1996; Breitner et al., 1995; Szekely et al., 2004; Stewart et al., 1997; Beard et al., 1998; Akiyama et al., 2000; In t'Veld et al., 2001). In particular, long-term NSAID therapy delayed the onset and progression of the disease, reduced symptomatic severity, and significantly slowed the rate of cognitive impairment (Rich et al., 1995), and at least one early treatment study with indomethacin suggested modest benefit in a small number of AD patients (Rogers et al., 1993). The epidemiological literature suggests an association between treatment duration and response for NSAIDs in preventing AD, with at least 2 years of exposure necessary to obtain full benefit (Breitner and Zandi, 2001). Thus, the benefit may be greater the longer NSAIDs are taken (Etminan et al., 2003). Studies from aged controls and postmortem AD patients, both on reported NSAD medication, show that long-term NSAID therapy reduces the degree of plaque associated inflammation (Alafuzoff et al., 2000; Mackenzie and Munoz, 1998; Mackenzie, 2001).

Some of these beneficial effects have been further investigated in animal studies using APP overexpressing mice that display amyloid as well as inflammatory components of the disease. Several studies have demonstrated that the NSAID ibuprofen acts to reduce astrocyte and microglial activation and cytokine production in APP transgenic mice (Lim et al., 2000; Yan et al., 2003; Heneka et al., 2005b). Six-month treatment with NSAIDs in Tg2576 significantly delayed AD symptoms, including a decrease of 40–50% in amyloid deposition (Lim et al., 2000) and improved performance in behavioral tasks (Lim et al., 2001; Westerman et al., 2002). This effect was also observed in a short-term administration of a subset of NSAIDs to young Tg2576 APP mice, which lowered the soluble levels of Aβ1–42 (Eriksen et al., 2003; Weggen et al., 2001). Moreover, treatment in the same mice with Meclofen, S-flurbiprofen or indomethacin reduced both Aβ1–40 and Aβ1–42 levels (Eriksen et al., 2003). Additionally, it has been shown that long-term treatment with ibuprofen and indomethacin significantly decreased $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in both cortex and hippocampus of APP transgenic (Tg2576) mice (Yan et al., 2003; Sung et al., 2004).

To date, the underlying mechanisms by which NSAIDs prevent AD are unclear, however evidence for several mechanisms has been put forward and there is the distinct possibility that actions at multiple rather than a single level of AD relevant pathology account for the observed beneficial effects of NSAIDs. Potential mechanisms include:

(1) Protection against Aβ aggregation: it has been shown that certain NSAIDs may alter the β-sheet conformation of Aβ affecting the aggregation of Aβ peptides *in vitro* (Agdeppa et al., 2003; Thomas et al., 2001). Another report indicates that NSAIDs could induce the expression of amyloid binding proteins such as transthyretin, subsequently decreasing Aβ aggregation (Ray et al., 1998).
(2) Effect on amyloid precursor protein (APP processing: the protective effect of NSAIDs has been associated with decreased production of Aβ and soluble APP, although there is still debate about the molecular mechanism involved (Blasko et al., 2001; Weggen et al., 2001; Sastre et al., 2003). In particular, a subset of NSAIDs appears to directly affect the generation of $A\beta_{1-42}$, which is the most amyloidogenic form of Aβ. This subset of NSAIDs was shown to shift the cleavage products of APP to shorter, less fibrillogenic forms (Weggen et al., 2001), indicating that NSAIDs could have an allosteric inhibitory effect on γ-secretase by altering PS1 conformation (Lleo et al., 2004).
(3) Inhibition of an alternate pathway: ibuprofen has been shown to reduce pro-amyloidogenic α1-antichymotrypsin, an effect likely mediated by decreasing IL-1β (Morihara et al., 2005).
(4) Inhibition of cyclooxygenases: the canonical targets of NSAIDs are COX-1 and -2. Prostaglandin E_2 levels are increased 5-fold in the CSF of probable AD patients (Montine et al., 1999) and COX-2 products are associated with neurodegeneration (Kawano et al., 2006).
(5) Several NSAIDs target the peroxisome proliferator activated receptor gamma (PPARγ) (Lehmann et al., 1997), a nuclear hormone receptor studied for more than a decade by endocrinologists for its ability to increase insulin sensitivity (Vamecq and Latruffe, 1999; Patsouris et al., 2004). As described in more detail below, some of the beneficial effects ascribed to NSAID medication may be mediated by PPARγ activation.

Despite these multiple mechanisms, recent clinical trials with selective COX-2 inhibitors and the mixed COX-1/COX-2 inhibitor naproxen have been uniformly disappointing (Aisen et al., 2003; Reines et al., 2004; Thal et al., 2005). This suggests that pathological changes may be too far advanced by the time of clinical diagnosis. Alternatively, off-target effects of NSAIDs may be critical and not maximally achieved with the specific drugs used in recent trials. Along these lines, neither COX-2 inhibitors nor naproxen inhibit $A\beta_{1-42}$ generation *in vitro* or *in vivo* (Eriksen et al., 2003).

10.2. PPARγ as target for NSAIDs

Ibuprofen, indomethacin and naproxen are among the five most prescribed NSAIDs, which have potentially decreased the risk for AD (In t'Veld et al., 2001). Interestingly, they are all agonists of the PPARγ (Lehmann et al., 1997). PPARs represent ligand-activated transcription factors that belong to a nuclear receptor superfamily and two isoforms, i.e. $PPAR\gamma_1$ (Kliewer et al., 1994) and $PPAR\gamma_2$ (Tontonoz et al., 1994) are formed from the same gene by alternative mRNA splicing. $PPAR\gamma_2$ is specifically expressed in adipose tissue and differs from $PPAR\gamma_1$ by the presence of 30 additional N-terminal amino acids that confer a tissue-specific transactivation function. $PPAR\gamma_1$ is the predominant, if not the only, isoform in all other tissues, including skeletal muscle and liver (Li et al., 2000).

PPARγ forms heterodimers with retinoid X receptors (RXR) (Tugwood et al., 1992) and upon ligand activation, the PPAR/RXR heterodimer recruits coactivators and binds to sequence-specific PPAR response elements (PPRE) present in the promoter region of several target genes (Tugwood et al., 1992). Alternatively, PPARγ can inhibit specific gene expression without direct binding to the gene promoter, since transrepression of several genes, i.e. iNOS and COX-2, is achieved in part by antagonizing the activities of transcription factors STAT1, NF-κB and AP-1 (Li et al., 2000; Daynes and Jones, 2002; Kelly et al., 2004; Heneka et al., 2003).

PPARγ is involved in several cellular functions, including control of glucose homeostasis, regulation of systemic insulin sensitivity, cell differentiation and cholesterol metabolism (Vamecq and Latruffe, 1999; Patsouris et al., 2004). The PPARγ gene knockout animal is embryonic lethal, due to essential roles in adipose, kidney and placental development (Barak et al., 1999). A role in the regulation of immune and inflammatory responses was suggested by the findings that PPARγ is expressed in macrophages and that receptor activation results in the inhibition of various inflammatory events, such as the production of IL-1β, TNF-α, IL-6 and iNOS (Ricote et al., 1998; Jiang et al., 1998). PPARγ also appears to be involved in proliferation and production of IL-2 by T-lymphocytes and IFN-γ expression in murine CD4 and CD8 cells (Cunard et al., 2004).

In the brain, several anti-inflammatory effects of NSAIDs may be in part mediated through the activation of PPARγ (Landreth and Heneka, 2001), since it has been shown that PPARγ agonists protect neurons from cytokine-mediated death (Heneka et al., 1999). Combs et al. reported that PPARγ agonists, including ibuprofen, inhibited Aβ-mediated microglial activation and neurotoxicity using *in vitro* models (Combs et al., 2000). Similar anti-inflammatory effects of PPARγ agonists and ibuprofen were also observed following infusion of immunostimulants into rodent brain (Heneka et al., 2000). In line with these findings, recent studies have documented the salutary effects of PPARγ-agonists in animal models of multiple sclerosis (Feinstein et al., 2002a; Niino et al., 2001; Diab et al., 2002; Natarajan and Bright, 2002) and Parkinson's disease (Breidert et al., 2002; Dehmer et al., 2004). The potent anti-inflammatory effects of PPARγ-agonists suggest that they may have beneficial effects in treating other CNS diseases with an inflammatory component.

PPARγ activation is achieved by binding to a specific receptor binding pocket by various endogenous and synthetic ligands (Lehmann et al., 1997; Yki-Jarvinen, 2004). Thus, PPARγ is stimulated best by 9-HODE (hydroxyoctadeca-9Z,11E-dienoic acid, 13-HODE and 15-deoxy-Δ12,14-prostaglandin J_2 ($15dPGJ_2$, although there is now considerable controversy as to whether 15d-PGJ_2 is actually a biologically relevant PPARγ activator or the majority of its action is mediated by inhibition of IκB kinase (IKKα and subsequently NFκB activation (Rossi et al., 2000). However, it has been reported recently that 15d-PGJ_2 is produced *in vivo*, and in large quantities by macrophages *in vitro*. Synthetic PPARγ ligands are used for their potent antidiabetic effects. In the United States, two ligands of the thiazolidinedione (TZD class, rosiglitazone and pioglitazone, have been approved for the treatment of NIDDM. Both substances bind PPARγ with high affinity and enhance insulin-mediated glucose uptake by increasing insulin sensitivity. In addition to receptor mediated effects some of these substances exert antiinflammatory effects independently of PPARγ activation (Chawla et al., 2001; Feinstein et al., 2005).

Two *in vivo* investigations on the effects of PPARγ activation in APP transgenic mice have been reported. An acute 7-day oral treatment of 10-month-old APPV717I mice with the PPARγ agonist pioglitazone or the NSAID ibuprofen resulted in a reduced number of activated microglia and reactive astrocytes in the hippocampus and frontal cortex (Heneka et al., 2005b). Drug treatment reduced expression of the proinflammatory enzymes COX-2 and iNOS and the levels of BACE1. The same mice presented decreased Aβ42 levels, while a non-statistically significant reduction of about 20–25% in Aβ40 levels was found (Heneka et al., 2005b). Furthermore, intracellular Aβ staining was reduced in mice treated with ibuprofen or pioglitazone, indicating that PPARγ activation is involved in the regulation of Aβ generation (Sastre et al., 2006). A different study indicated that treatment of 11-month-old Tg2576 mice overexpressing human APP with the NSAID

ibuprofen and PPARγ agonist pioglitazone for 16 weeks, only modestly reduced SDS-soluble Aβ levels and did not affect amyloid plaque burden (Yan et al., 2003). Since only 20% of pioglitazone crosses the blood brain barrier, and the study by Heneka et al. utilized twice the concentration used by Yan and colleagues (Yan et al., 2003; Heneka et al., 2005b), the observed difference may be explained by the drug concentrations applied.

All PPARs have been shown to be present in the CNS and to exhibit both unique and overlapping patterns of expression in various areas and at different developmental stages. The levels of expression of PPARγ in post-mortem brain sections from AD patients have been examined (Sastre et al., 2006) and immunohistochemical assessment of frontal cortex revealed that PPARγ is expressed in astrocytes and neurons. It has previously been suggested that AD brains contain increased levels of PPARγ in the cytosolic fraction compared to healthy controls (Kitamura et al., 1999). These results are in contrast with our own analysis showing a 40% reduction of PPARγ protein levels in AD patients compared to controls. In addition, PPARγ protein levels and its binding to a PPRE in the BACE1 promoter were decreased in AD brains (Sastre et al., 2006). Combined, these findings point to a direct role of PPARγ in the regulation of BACE1 transcription and activity in AD, ultimately facilitating Aβ generation.

11. Conclusions and future directions

Increasing evidence suggests that inflammation significantly contributes to the pathogenesis of AD. The generation and secretion of proinflammatory mediators may interact at multiple levels with neurodegenerative mechanisms. Thus, several proinflammatory cytokines cannot only induce neuropathic mechanisms and thereby contribute to neuronal death, but are also able to influence classical neurodegenerative pathways such as APP processing. The concomitant release of antiinflammatory mediators may partly antagonize this action ultimately contributing to the chronicity of the disease. Several AD specific mechanisms such as locus ceruleus and nucleus basalis Meynert cell death may facilitate the occurrence of neuroinflammation. Future studies need to determine the underlying mechanisms and means by which the course of the disease can be influenced. Additional information on how inflammatory mediators and excitotoxic factors potentiate their detrimental effects is required. Additionally, more information is needed regarding the extent to which inflammatory mediators functionally impair cognition and memory.

Clinically, novel approaches to visualize early neuroinflammation in the human brain are needed to improve the monitoring and control of therapeutic strategies that target inflammatory and other pathological mechanisms. Similarly, more insight in the role of genetic factors that transmit a disposition for the disease should improve the detection of people at risk to develop AD.

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