[Frontiers in Bioscience, 3, d436-446, April 16, 98]

# THE ESSENTIAL ROLE OF INFLAMMATION AND INDUCED GENE EXPRESSION IN THE PATHOGENIC PATHWAY OF ALZHEIMER S DISEASE

**Lars Nilsson[1], Jack Rogers[2] and Huntington Potter[1]**

*Department of Neurobiology[1], Harvard Medical School and Division of Hematology, Department of Medicine[2], Brigham and Women s Hospital, Harvard Medical School, Boston, MA 02115, USA*

Received 3/30/98 Accepted 4/3/98

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## 1. ABSTRACT

Alzheimer's disease is among the most common diseases of advanced age affecting almost one out of ten individuals who survive beyond the age of 65 years, and an another 10% for each additional decade of the life-span. The prognosis of the disease is an inexorable decline of mental functions leading to complete dependence on caretakers in the late stages of the disease. Alzheimer's disease will become a steadily increasing financial health-care problem in the industrialized world with the increasing longevity and ageing of the population. To-date there are no effective therapeutics. However, during the last years promising findings suggest that anti-inflammatory treatment strategies might be efficient. Here, we will review the experimental and epidemiological findings which support the idea that inflammatory mechanisms play an important role in Alzheimer's disease pathogenesis. The review of the experimental findings will be focussed on the amyloid-associated proteins, $alpha_1$-antichymotrypsin and apolipoprotein E, as well as the major cytokines. In addition, the epidemiological studies on non-steroidal anti-inflammatory drugs and traumatic head injury will be summarized. We hypothesize a pathogenic model for Alzheimer's disease in which the expression of amyloid-associated proteins/pathological chaperones, induced by inflammatory cytokines, plays an essential role in accelerating the disease progress, and suggest potential targets for drug discovery based on such a model.

## 2. INTRODUCTION

Alzheimer's disease is a devasting neurodegenerative disorder clinically characterized by an insidious onset, a progressive decline of multiple cognitive functions, and ultimately fatal loss of mental functions. The disease is defined by characteristic neuropathological lesions – proteinaceous deposits – which are primarily found in the hippocampus and the parietotemporal parts of the cerebral cortex. These lesions are the neuritic plaques, which are largely composed of extracellular deposits of beta-amyloid peptides, and the intraneuronal neurofibrillary tangles consisting of twisted filaments of the cytoskeletal tau protein.

During the last five years, Alzheimer's disease research has been greatly benefited by molecular genetic discoveries of pathogenic genes, which have allowed us to begin to decipher the molecular mechanisms of the disorder. Initially, missense mutations in the amyloid precursor protein (APP) gene were found, although these cases were extremely rare (1-2). Two more recently identified pathogenic genes, presenilin-1 and presenilin-2, account for a much larger portion of the early-onset familial cases (3-7). These findings have brought the metabolism of the amyloid precursor protein, a ubiquitously expressed transmembrane protein, into focus for two reasons. Cleaved fragments of the amyloid precursor protein, beta-amyloid peptides, are the major constituents of the amyloid deposits (8-9), and all Alzheimer pathogenic mutations have been shown to increase the production of beta-amyloid, in most cases by generating more of the longer beta-amyloid peptides 1-42(43) (10-12). Thus therapeutic strategies aimed at intervening in the formation of beta-amyloid peptides or the aggregation of beta-amyloid filaments have been suggested (13-16). The major obstacle to these strategies is the nonspecific mechanism by which beta-amyloid peptides probably are generated (17) and the rapid turnover rate of the amyloid precursor protein (18).

It has become increasingly appreciated that inflammatory mechanisms in the brain are as important as beta-amyloid production in the Alzheimer pathogenic pathway, and that these mechanisms perhaps are more promising drug targets. The evidence that anti-inflammatory treatment strategies would be beneficial comes from epidemiological and experimental findings. Here we will review this literature in the context of a model for the Alzheimer pathogenic pathway in which expression

of amyloid-associated proteins/pathological chaperones, orchestrated by inflammatory cytokines, plays an essential role in accelerating the disease progress.

## 3. AMYLOID-ASSOCIATED PROTEINS

The first hint that Alzheimer's disease pathology might involve an inflammatory reaction came from the observation of reactive astrocytes and microglia in affected brain regions in the initial neuropathological description (19). However the absence of standard features of inflammation such as swelling and lymphocyte infiltration argued against this description. The breakthrough came in the 1980's when the Alzheimer amyloid deposits were found to contain, in addition to beta-amyloid peptides, other proteins that are normally observed during inflammation and its associated acute phase response. Activated complement components were the first such inflammation-associated proteins identified in the Alzheimer amyloid deposits (20). However, it was quite possible that such proteins had leaked into the brain from the circulation and were not indicative of an endogenous inflammation in the brain. Soon thereafter, our lab showed that the acute phase protein alpha$_1$-antichymotrypsin (ACT) was an integral component of the amyloid filaments (21). ACT formed stable complexes with beta-amyloid peptide *in vitro,* that were resistant to boiling in SDS and beta-mercaptoethanol (22-23). Furthermore ACT was found to be specifically associated with beta-amyloid containing deposits but not with other types of amyloidosis (24), and to be generated through overexpression from astrocytes surrounding the plaque structures (25-26). ACT levels in serum and cerebrospinal fluid (CSF) have been suggested as diagnostic markers for Alzheimer's disease, since elevated levels have been observed in AD but not in other neurodegenerative disorders (27-29), while at the same time various other acute phase proteins have been found unchanged (30). The serum and CSF levels have not been found to correlate, indicating that serum ACT is most probably derived from the periphery. The increase in serum levels of ACT is likely not a very early marker of Alzheimer's disease, since normal levels have been found in young Down's syndrome patients (31-32).

Another primarily astrocyte-derived protein of clear relevance for Alzheimer disease pathology, and possibly reflective of inflammatory mechanisms, is apolipoprotein E (apoE). This lipoprotein was early-on detected in amyloid plaques of the brain parenchyma with immunohistochemistry (33-34). However apoE did not receive major attention until Allen Roses and Judes Poirier and their coworkers highlighted it as an beta-amyloid binding protein in the cerebrospinal fluid, and the ApoE4 allele as a susceptibility gene for the development of Alzheimer's disease (35-37). In addition, Poirier and coworkers discovered that apoE serves important functions with respect to cholesterol and phospholipid metabolism following injury of the central nervous system (38). Later studies have confirmed that apoE forms stable complexes with beta-amyloid *in vitro* as well as in purified amyloid filaments from Alzheimer disease brain (39), and that the apoE4 allele is a major risk factor for late-onset Alzheimer's disease (40).

## 4. CYTOKINES

Because glial cell activation is such a prominent feature of Alzheimer disease pathology, substances with the ability to promote or modulate these changes were early investigated. Cytokines belong to a growing family of polypeptides associated with injury and inflammatory responses in the periphery as well as in the central nervous system. They are present at very low concentrations under normal physiological conditions and are rapidly induced during various pathological states. High-affinity cytokine receptors allow low concentrations of released cytokine to exert potent effects, which can be either beneficial or detrimental to neuronal survival. For instance, interleukin-1 (IL-1) has been shown to protect neurons from excitotoxic damage by release of nerve growth factor *in vitro* (41). However, a substantial literature implicates the IL-1-cleaving enzyme (ICE) and other homologous caspases in apoptotic cell death (42).

The cytokine which has been most studied and implicated with respect to Alzheimer disease pathology is interleukin-1 (IL-1). IL-1 was early-on shown to stimulate astroglial proliferation and angiogenesis in response to traumatic injury through its secretion from ameboid microglia in the rat brain (43-45). Furthermore IL-1-containing microglia were found to be 30-fold more abundant in Down syndrome brain and 6- fold more abundant in Alzheimer's disease brain as compared to control brain (46). Interestingly, this induction was restricted to resident microglia in brain regions that normally develop mature neuritic plaques, but not in cerebellum where mostly diffuse plaques are seen. (47-48). Furthermore IL-1 was shown to upregulate APP-mRNA expression in endothelial cells through a protein kinase C dependent pathway that was targetted to a 180bp region in the APP-promoter (49). IL-1 has recently been shown to upregulate the translational efficiency of APP-mRNA in astrocytes via a stem-loop structure in the 5'UTR of the APP-transcript (50).

IL-6 is a multifunctional cytokine and the other main pro-inflammatory signaling molecule linked to Alzheimer's disease pathology. It is the principal inducer of plasma proteins during the hepatic acute phase response—a homeostatic mechanism to limit protease degradation in the aftermath of injury, trauma, or infection (51). Elevated levels of IL-6 have been found in Alzheimer's brain and cerebrospinal fluid (52-55), and this induction appears to occur concurrently with early stages of senile plaque formation (56). The findings from *in vivo* studies on the effect of overexpression of IL-6 in the brain is contradictory. Astrocyte-targeted IL-6 overexpression has been shown to cause marked neurodegeneration and learning impairments (57-58), while IL-6 expression under the control of the neuronal-specific enolase promoter led to astrogliosis in the absence of neurodegeneration or behavioral changes (59).

TNF-alpha is another major pro-inflammatory cytokine found in the brain. Increased levels of TNF-alpha has been reported after head injury (60). The functional significance of TNF-alpha in terms neurodegeneration/-protection is unclear. Cytotoxic effects on oligodendrocytes in experimental models of autoimmune diseases have been described (61-62). However, TNF-alpha receptor knockout mice displayed suppressed microglial activation, greater neuronal loss and larger cortical infarct area than normal mice, suggesting a neuroprotective role for TNF-alpha against seizure and ischemia-induced damage (63). TNF-alpha-positive cells have not been observed in Alzheimer's disease brain (64-65), and serum measurements are conflicting (66-67).

Astrocyte expression of TGF-beta$_1$, an anti-inflammatory cytokine, has recently been linked to beta-amyloid deposition in the cerebral blood vessels and meninges (68), that resemble the cerebral amyloid angiopathy (CAA) which is frequently found in Alzheimer's pathology (69-70). Previous transgenic experiments have demonstrated that this cytokine dose-dependently upregulates extracellular matrix proteins, which might be the mechanistic link to the amyloid deposition (71). TGF-beta$_1$ has also been identified in subsets of amyloid plaques (72).

Various other proteins such as complement proteins (73), acute phase reactants (52) and proteoglycans (74) have been demonstrated in amyloid plaques, in most cases with immunohistochemistry. The significance of these markers has previously been extensively reviewed (75). These plaque-associated proteins are, like ACT, apoE and IL-1, mainly derived from microglia and astrocytes, cell categories which play important functions in regeneration and immune functions of the central nervous system.

## 5. EPIDEMIOLOGY

Epidemiological studies on the use of non-steroidal anti-inflammatory drugs (NSAID) and on traumatic head injury provide further evidence for inflammatory mechanisms as being important for Alzheimer's disease. Besides the currently-established risk factors for Alzheimer's disease—age, apoE genotype, and family history of dementia—there is growing evidence for a previous history of head injury as a contributor to the disease development. These findings come from retrospective case-control studies (76-78) as well as prospective incidence studies (79). Furthermore an Alzheimer-like pathology, dementia pugilistica, can be generated by the repeated head injury that boxers experience (80-82). A mechanistic link is indicated by morphological studies showing that suspected contributors to Alzheimer's neuropathology such as IL-1-alpha-positive microglia (83) and beta-amyloid deposition (84) are observed in the acute phase of head trauma in human brain. Other studies suggest an interaction with a known genetic risk factor for Alzheimer's disease by showing that the trauma-generated beta-amyloid deposition is dependent upon the presence of the apoE4 allele (85).

A number of pharmaco-epidemiological studies support the routine use of NSAID as therapeutic of Alzheimer's disease. Initially two reports suggested that patients suffering from inflammatory diseases such as rheumatoid arthritis had a reduced incidence of Alzheimer's disease (86-87). The explanation for the results, as suggested by the authors, was that the anti-inflammatory drugs routinely used by these patients exerted a protective effect against the development of Alzheimer's disease. Alternative interpretations of the findings were possible since the studies were prone to methodological problems such as selection bias and/or under-reported frequency of Alzheimer's disease among the rheumatoid patients by the clinicians. However most probably anti-inflammatory drugs exert a truly protective effect since these early studies have been reproduced in larger experimental settings (88-90) and by alternative methods such as co-twin control studies (91). Indeed, initial clinical trials have demonstrated that the inflammatory drug indomethacin exerted beneficial effects on Alzheimer patients with respect to cognitive decline (92). Larger prospective studies are currently underway to test whether routine use of anti-inflammatory agents by Alzheimer patients will have significant therapeutic benefits.

## 6. PATHOLOGICAL CHAPERONES THE ACCELERATOR HYPOTHESIS

A unifying hypothesis for the Alzheimer's disease pathology would be helpful in order to get a comprehensive view of the various findings so far discussed. Currently, the leading model for the ethiology of Alzheimer´s disease is the amyloid hypothesis/amyloid cascade hypothesis (13, 93-94) which states that overproduction or insufficient clearance of beta-amyloid fosters the deposition and formation of amyloid plaques as the central event of the pathology. The deposition then causes tau phosphorylation, tangle formation, subsequent neuritic degeneration, and ultimately the clinical symptomatology. One major pitfall with this hypothesis is its inability to explain the apparent region-specificity of Alzheimer´s disease. Furthermore the density of amyloid plaques is not well correlated with cognitive decline (95). Most probably the latter is due to the fact that amyloid plaques are neuropathologically heterogeneous and that only subtypes such as the paired helical filament (PHF)-containing neuritic plaques are detrimental to neuronal survival. Thus it seems likely that additional mechanisms e.g. cofactors released downstream of the initial beta-amyloid aggregation are essential for disease development. Gliosis is a prominent feature of Alzheimer's pathology, with both activated microglia and reactive astrocytes being clearly visible in the periphery surrounding the amyloid core structure (19, 96-98). These changes have often been viewed simply as a secondary tissue response to the ongoing amyloidosis without any etiologic significance. Here we reiterate and extend our model of the pathogenic pathway in Alzheimer's disease which postulates that cytokines and amyloid associated proteins released by these cells accelerate the beta-amyloid aggregation-transforming and stabilizing the amyloid filaments to form cores of mature senile plaques (21-23, 47, 99, 16).

The initial step in this pathogenic pathway is the accumulation of beta-amyloid peptides into amorphous deposits. There is an apparent consistency in the *in vitro* fibrillogenesis studies (100-101), the *in vivo* data from Alzheimer's disease brain (102-103), and the temporal examination of Down syndrome brains (104-105), in that the longer beta-amyloid peptide(1-42) is the most amyloidogenic and earliest deposited. This initial deposition probably acts as seed for further deposition of shorter and less amyloidogenic peptides, such as beta-amyloid(1-40) (106).

The second step in the pathway is the reactive expression of inflammation-related proteins in association with amyloid deposits. There is histopathological evidence that IL-1 (107) as well as IL-6 (56) - immunoreactivity in the cerebral cortex is preferentially associated with early stages of plaque evolution when the beta-amyloid aggregation is mostly of the diffuse type, rather than mature plaques with the classic congophilic dense core. Microglial activation and proliferation in amyloid plaque-forming areas has also been described in the $APP_{sw}$ transgenic strain (108). Perhaps some beta-amyloid aggregate with a low level of the characteristic beta-sheet structure observed in the diffuse deposits is sufficient to induce the microglial activation and cytokine production.

The third step of the cascade is the production and release of amyloid-associated proteins that accelerate amyloid filament formation—the pathological chaperones. It has long been known that the transcriptional induction of the peripheral acute-phase response in the liver is mediated by IL-1 and IL-6 (109). Results from our lab demonstrated that the ACT-overexpression in astrocytes of Alzheimer's disease brain is likely caused by cytokines as well. Specifically ACT mRNA was 3-5-fold upregulated by IL-1 in mixed glial cells of human fetal origin. Interestingly, the ACT mRNA expression was found to be both species- and brain region-dependent. The rat gene homologue of ACT, contrapsin, was not induced by either IL-1 or IL-6. Furthermore human cerebral cortical, but not cerebellar or brain stem mixed glial cultures were able to spontaneously express IL-1 and ACT, suggesting that the mechanisms for the region specificity of Alzheimer's disease pathology may reflect differences in glial cell functioning (47-48). Whether the apoE gene is inducible in a corresponding fashion, and if so by which putative regulatory factors is largely unknown, although overexpression of apoE mRNA was early demonstrated in Alzheimer's disease brain (110). Certainly the synthesis of apoE mRNA is increased following peripheral nerve injury (111-113) and entorhinal-cortex lesion–a model for reactive synaptogenesis and compensatory reinnervation of the hippocampus (114-115). Association between a polymorphic site in the apoE promoter and Alzheimer's dementia also stresses the importance of regulation of apoE gene expression in the disease process (116).

Another link between IL-1 and Alzheimer pathology is the ability of IL-1 to increase the translational efficiency of the amyloid precursor protein (APP) in astrocytes by means of a stem-loop structure in the 5'UTR of the APP-transcript (50). Thus astrocytes in the vicinity of a developing amyloid plaques, overproduce not only the amyloid associated proteins apoE and ACT, but also the APP protein (and therefore the beta-amyloid as well). Indeed, increased APP protein levels have been detected *in vivo* following IL-1 injection into the rat brain parechyma (117).

Given the close association of apoE and ACT with the Alzheimer amyloid deposits, it was reasonable to determine whether these proteins influenced the formation of amyloid filaments. Results from our and other labs have demonstrated that beta-amyloid filaments form much more rapidly in the presence of the amyloid-associated proteins ACT or apoE (99, 118-120). Instead of days, filaments formed in a matter of hours and grew to very great lengths. Particularly interesting was the fact that apoE4, the apolipoprotein E isoform which is linked to late-onset familial Alzheimer's disease (40), was the most effective amyloid promoting factor (99). There is now an abundant literature on the role of apoE and ACT as amyloid promoting factors. The concept of pathological chaperones (a term coined by Wisniewski and Frangione, 34) is not yet fully established, since some *in vitro* studies are partly contradictory (121-123). However the discrepancies are probably due to methodological differences in terms of the amyloid peptide used (beta-amyloid(1-40) versus beta-amyloid(1-42)), the quality and purity of the beta-amyloid peptide preparations, and the molar ratio of beta-amyloid to the chaperone used. Indeed, a recent *in vivo* study has unequivocally demonstrated that apoE is an amyloid promoting factor. Specifically, mice strains carrying zero, one, or two copies of the mouse apoE gene on the backgound of the PDAPP-transgenic mouse strain showed an apoE dose dependent increase in beta-amyloid deposition in cerebral cortex and the hippocampus, strongly supporting the chaperone concept. The beta-amyloid peptide was relatively harmless and essentially unable to polymerize efficiently into amyloid filaments in the absence of apoE (124). The demonstration of accelerated cerebrovascular amyloid deposition achieved by crossing a GFAP/TGF-$beta_1$ -low-expressing mouse strain with the PDAPP-transgenic strain also supports the idea that cofactors are involved in amyloid deposition, in this case possibly mediated via expression of extracellular matrix proteins (68). It has recently been clinically shown that the ACT/A-allele, which is a suspected genetic risk factor for Alzheimer disease (125), is dose-dependently associated with higher load of amyloid angiopathy in Alzheimer's patients, as measured by Congo Red staining (126). Thus increased secretion of ACT might promote amyloid deposition in the cerebral vessels and meninges as well as in the brain parenchyma.

The mature amyloid deposits induce tangle formation, neuritic degeneration and ultimately neuronal loss. These final steps in the Alzheimer pathogenic pathway remain rather undefined, since the mechanisms for neurodegeneration and neuronal death in Alzheimer's disease are essentially unknown. Mature amyloid filaments could exert direct neurotoxic effect as demonstrated *in vitro* (127-128, 16), although no neuronal loss was observed in

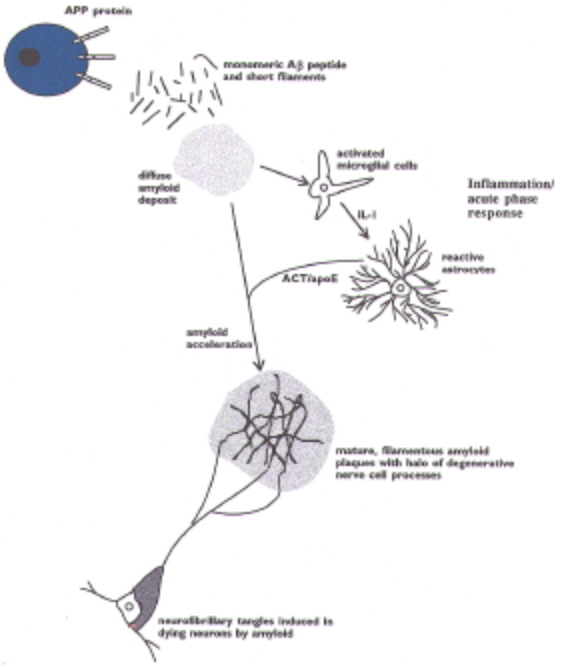


**Figure 1.** Pathogenic pathway for Alzheimer's Disease. The earliest and most widespread pathological change in Alzheimer's disease is the accumulation of beta-amyloid peptides into amorphous deposits. The deposition induces an inflammatory reaction and consequently an acute phase response involving IL-1 and IL-6 in microglial cells of the brain parenchyma and TGF-beta$_1$ in perivascular astrocytes. The cytokines trigger release of various secretory products from the surrounding astrocytes that catalyze the transformation of diffuse beta-amyloid in amorphous deposits into mature amyloid filaments. For example astrocyte production of beta-amyloid and pathological chaperones such as ACT and apoE accelerate the polymerization of beta-amyloid peptides into filaments. Extracellular matrix proteins may stabilize the amyloid structures. Finally neurons of the human brain respond to the glial activation and the mature amyloid deposits by tangle formation, subsequent neuritic degeneration and ultimately cell death.

the PDAPP mice in spite of heavy congophilic amyloid load (129). The necessity for intraneuronally directed beta-amyloid deposition has been suggested, however this hypothesis remains unproven and speculative (130-131). Perhaps there is a species difference in the way human neurons respond to amyloid deposits and the mounted gliosis, since tangle formation, morphologically similar to those of Alzheimer's disease is human specific. Such an hypothesis could be tested by grafting primary human fetal neurons into any of the to-date-available transgenic strains producing congophilic plaques, or by mating a human tau transgenic mouse with the PDAPP mouse. A recently – performed *in vivo* study supports this view by showing differential neurotoxic effects of beta-amyloid in the primate and rat brain respectively (Yankner, personal. comm.).

The pathogenic pathway for Alzheimer's disease shown in "figure 1" provides an explanation for the experimental and epidemiological findings linking the disease development to injury and inherent inflammatory mechanisms of the central nervous system. Furthermore it exposes several potential targets for drug discovery. For instance most of the detrimental effects of gliosis would be inhibited at an early stage if microglial activation in general, or that induced by beta-amyloid filaments, were suppressed (132-133). Substances that lower the biosynthesis of cytokines or the pathological chaperones and/or inhibit the actions of cytokines, such as IL-1 or IL-6 receptor antagonists or ICE-inhibitors could be valuable drug candidates. Designed ligands that stabilize the recently identified stem-loop structure in the 5'UTR of the APP-mRNA and thereby mediate translational inhibition of the amyloid precursor protein in astrocytes should possibly lower beta-amyloid production and fibril formation. Furthermore, ligands that specifically block the interaction of beta-amyloid with the pathological chaperones, apoE or ACT, would have the ability to significantly retard the polymerization process (16). These putative therapeutic strategies would all have the potential to significantly delay the progress of Alzheimer's disease.

## 7. ACKNOWLEDGEMENT

Postdoctoral fellowships from the STINT- foundation and Riksbankens Jubileumsfond, following a donation from Erik Rönnberg were greatly acknowledged (L.N.).

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**Key Words:** Alzheimer's Disease, $Alpha_1$-Antichymotrypsin, Apolipoprotein E, Beta-Amyloid, Chaperone, Cytokine, Gene Expression, Inflammation

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Send correspondance to: Huntington Potter, Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA, Tel: (617)-432-0751, Fax: (617)-734-7557, E-mail: hpotter@warren.med.harvard.edu