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Reactive astrocytes and α1-antichymotrypsin in Alzheimer's disease☆

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Abstract

There is ample genetic, biochemical, cellular and molecular evidence to show that the amyloid β peptide (Aβ), a proteolytic fragment of the amyloid precursor protein (APP), plays an important, if not causative role in Alzheimer's disease (AD). An additional hallmark of AD is the neuroinflammatory response that is associated with the amyloid deposition. We discovered that the acute phase protein α1-antichymotrypsin (ACT) is overexpressed by reactive astrocytes, and is tightly associated with virtually all amyloid plaques in the AD brain. It has also been shown that Aβ and ACT bind in vitro. Recently, we have reported that astrocytic expression of ACT in APP transgenic mice leads to an increased plaque deposition in ACT/APP doubly transgenic mice compared to the APP mice alone, suggesting that ACT interferes with Aβ clearance. The main objective of this review is to summarize the role of astrocytosis and ACT in the pathogenesis of AD.

Keywords: Acute phase proteins; α1-antichymotrypsin; Apolipoprotein E; Cytokines; Animal models of AD; Amyloid β protein; Neuroinflammation

1. Introduction

Alzheimer's disease (AD) neuropathology is characterized by the abnormal accumulation of extracellular amyloid in plaques and in cerebral vasculature, intraneuronal neurofibrillary tangles, dystrophic neurites, neuronal and synaptic losses in selected brain areas, and the appearance of reactive astrocytes and activated microglia. For review see [49].

Longitudinal neuropathological studies on Down syndrome (DS) patients, who develop AD pathology if they live beyond 40 years of age, reveal that the first detectable feature is the appearance of amyloid plaques [46]. This is followed years later by the other AD hallmarks, i.e. neurofibrillary tangles and astrocytosis. Similar development of AD-like pathology has been also observed in transgenic mice models of AD (see below).

The major protein component of amyloid plaques is the amyloid β peptide (Aβ). Aβ is a proteolytic fragment produced from the amyloid precursor protein (APP) by the sequential actions of beta-site APP cleaving enzyme (BACE) at the N-terminus of Aβ and γ secretase at its C-terminus (for review see [13]).

Aβ peptides exist as two major forms: one of 40 and one of 42 amino acid in length. Aβ42 has a higher tendency to aggregate and once aggregated is more resistant to degradation by extracellular proteases [54]. In the familial forms of AD caused by mutations in APP and presenilin 1 (PS1) and presenilin 2 (PS2) the ratio in blood of Aβ42 to Aβ40 is higher than in sporadic AD or controls. Higher Aβ42 levels correlate well with an earlier age of onset (for review see [56]) strengthening the importance of Aβ42 in AD pathogenesis. Thus, at least in familial AD, accumulation of Aβ42 could be the trigger for neurodegeneration, although a dysfunction of the mutated APP or PSs could also contribute to neuronal and synaptic loss.

Astrocytosis, also known as reactive gliosis, is one of the hallmarks of AD neuropathology that always accompanies the senile plaques, neurofibrillary tangles and selective neuronal loss [8,12]. The changes in astrocyte shape and function result from the new expression of genes and are likely a secondary reaction to the ongoing neurodegeneration. Astrocytosis is not limited to AD, but occurs in other neurodegenerative diseases such as Huntington's disease, Parkinson's disease, multiple sclerosis, prion diseases, AIDS dementia, and stroke [14]. Microglial cells in AD and in other brain disorders also become activated in response to neurodegeneration [38]. It is not clear whether astrocytes and microglia, both being brain phagocytic cells, are activated in parallel by the same or by different factors, but evidence suggests that microglia become activated first and

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then secrete cytokines that activate astrocytes. The activation of astrocytes and microglia is widely accepted as part of the brain's inflammatory reaction, and numerous studies show that inflammatory drugs may benefit AD patients or prevent altogether the onset of the disease [5,52]. The inflammatory process in neurodegeneration is distinct in that it lacks the immune cells and antibodies known to participate in peripheral inflammation [38].

Most of the studies describing astrocytosis use an antibody to the glial fibrillary acidic protein (GFAP) as a specific marker. GFAP is the building block of the astrocytic intermediate filaments. All astrocytes express GFAP, however when they react to certain environmental cues, they undergo cellular hypertrophy and express elevated levels of GFAP, among other genes. Thus, they become easier to detect and quantify. The phenotypic changes occur in resting astrocytes and they do not represent migration or proliferation of these cells (for review see [14]).

Examination of astrocytes in various species reveals that the aging process alone induces astrocytosis. Rodents [28, 31], monkeys [50] and humans [22] possess some level of astrocytic reactivity as a function of normal aging. However, the astrocytosis in AD is considerably more profound, especially in areas surrounding neuritic plaques.

1.1. What causes activation of astrocytes in AD?

There are two major hypotheses on what stimuli may induce astrocytic and microglial activation in normal aging, AD, and DS. The first implicates neurodegeneration in the form of neuronal or synaptic death. Microglia and astrocytes then phagocytose neuronal debris and become activated. But what causes neurodegeneration in the first place? Oxidative stress, complement attack, and the Aβ peptide have all been implicated in causing neurodegeneration. Another hypothesis suggests that Aβ directly activates microglia. These cells then produce inflammatory cytokines that induce the astrocytic expression of a plethora of acute phase proteins, proteases and their inhibitors, and a long list of proteins that participate in tissue repair (for review see [14]). At this time it is difficult to reconcile the exact order of events since it appears that a vicious cycle begins with aging and AD in the absence of a clear single trigger.

1.2. Does the activation of astrocytes have a positive or negative outcome?

Many classes of proteins are upregulated in reactive astrocytes (for review see [14]). The functional analysis of these molecules suggests that they are involved in repair of the injured neuronal tissue. For example, upregulation of proteases and protease inhibitors together with the expression of extracellular matrix and adhesion proteins could promote the remodeling of the extracellular matrix similar to these molecules' role in peripheral tissues. Expression of neurotrophic factors and transporter molecules for excitotoxic amino acids are crucial for the maintenance of a healthy milieu for the neurons. Apolipoprotein E (apoE), a lipoprotein produced in the brain mainly by astrocytes and upregulated in reactive astrocytes, is necessary for the transport and metabolism of lipids and cholesterol in neurons. ApoE has also been shown to bind Aβ (see below) [51]. Along with these potential benefits, detrimental effects of reactive astrocytes are also possible. In the process of brain tissue repair, the glial scar formed by hypertrophic astrocytes may form a barrier that could inhibit neurite outgrowth [44,45]. Moreover, an imbalance between proteases and their inhibitors in the favor of proteases could damage the brain environment by degrading the extracellular matrix and necessary growth factors. In summary, astrocytes could play protective and/or damaging roles in the brain. See Fig. 1.

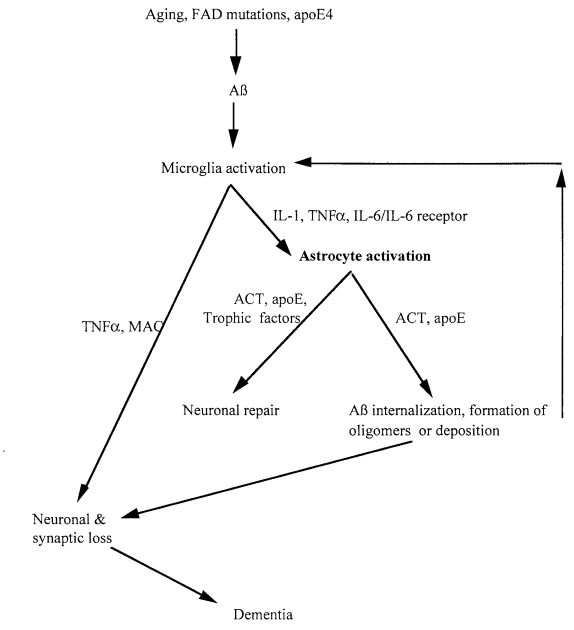

Diagram on the role of reactive astrocytes and ACT in the pathogenesis of AD.

MAC is the membrane attack complex produced by complement activation.

Note that the astrocytes play a central role in the delicate balance between neuronal repair and neuronal loss.

Fig. 1. Diagram on the role of reactive astrocytes and ACT in the pathogenesis of AD. MAC is the membrane attack complex produced by complement activation. Note that the astrocytes play a central role in the delicate balance between neuronal repair and neuronal loss.

1.3. Animal models for AD-related astrocytosis

Some of the roles attributed to reactive astrocytes that are relevant to AD can be analyzed in animal models. One such model is the transgenic mouse that overexpresses APP. Several transgenic mouse models have been produced in an effort to understand the sequence of events that lead to the AD neuropathology (for review see [23]). We have used in our studies the PDGF-APP mouse described by Games and colleagues [19]. These transgenic mice overexpress human

APP carrying the V717F mutation associated with familial AD. Their Aβ plaques become detectable in hippocampus and cortex between four and six months. Dystrophic neurites and neuritic plaques are present starting between eight to ten months of age. Astrocytosis begins at eight months and microgliosis at eight to ten months [10,19]. These studies demonstrate that Aβ deposition in mice precedes neuritic abnormalities, astrocytosis and microgliosis. Although the mouse pathology includes many of the changes occurring in the AD brain, such as senile plaques and synaptic loss, neurofibrillary tangles and neuronal loss are not present [37].

1.4. The role of the astrocytic protease inhibitor α1-antichymotrypsin (ACT) in AD

ACT is a serine protease inhibitor of the serpin family and an acute phase protein produced mainly by the liver and found in serum. We have discovered that ACT is tightly associated with Aβ in amyloid plaques and that ACT message is highly expressed in AD brain [2]. ACT was detected immunohistochemically in activated astrocytes during normal aging of humans and monkeys [3] and in several neurodegenerative diseases [4], suggesting that ACT overexpression is not limited to AD pathophysiology. *In situ* hybridization studies on AD brain revealed that ACT is produced mainly in reactive astrocytes around senile plaques [26,42]. The expression of ACT by cultured human astrocytes is induced by the proinflammatory cytokine IL-1 [11]. Additional factors that control the expression of ACT in astrocytes are TNFα, oncostatin M, and IL-6/soluble IL-6 receptor complexes [27,28]. Virtually all plaques, including diffuse plaques, were doubly stained with antibodies to Aβ and ACT [47], suggesting that ACT is found even in early diffuse plaques. This is not surprising since a few astrocytes are found in very early plaques [14]. Interestingly, although ACT upregulation is not AD-specific, the association of ACT with Aβ is specific. ACT was not detected in amyloid deposits occurring in other amyloidoses, suggesting that a special interaction occurs between ACT and Aβ [4]. Indeed, several investigators have provided evidence for the in vitro binding of ACT to Aβ [16,24,35] and the subsequent induction of fibrillogenesis [35]. In a subsequent study, Ma and colleagues showed that ACT increased the neurotoxicity of the Aβ peptide in parallel with its promotion of filament formation. Preincubation of ACT with small Aβ-related peptides abrogated their subsequent ability to promote both the formation and the neurotoxicity of Aβ filaments [34]. Nonetheless, there have also been reports suggesting that ACT binds to Aβ but induces Aβ fibril disaggregation [6,17].

In order to determine whether ACT has a protective or a detrimental effect in the pathogenesis of AD, we need to know which form of Aβ: monomeric, oligomeric or fibrillar, and which length of the peptide: 40 or 42 amino acids is the most toxic. Based on in vitro experiments using many cell types, it has been suggested that fibrillar Aβ is toxic while soluble Aβ is not (for review see [55]). Early studies showed that the toxic Aβ preparations contained abundant amyloid fibrils, although smaller species were also noted [32]. More recently there is accumulating evidence that soluble Aβ oligomers are synaptotoxic while fibrillar Aβ appears to be inert [25,33,39]. Brains of AD patients contain more than 30 fold the levels of soluble Aβ1–42 compared to the brains of cognitively normal 80 years olds [18]. Moreover, Lue et al. found that both soluble Aβ1–40 and 1–42 correlated inversely with changes in synaptic density while insoluble forms of Aβ did not [33]. If this proves to be the case, molecules previously called "pathologic chaperones" [53], such as ACT and apoE, that bind to Aβ and induce fibrillogenesis may actually sequester the toxic oligomeric type of Aβ. On the other hand, if fibrils are toxic, then overexpression of ACT and apoE by astrocytes may be detrimental. We have reported that when incubated in vitro with the three most prevalent isoforms of apoE, Aβ1–40 binds to nascent apoE in the following order apoE2 $>$ apoE3 $\gg$ apoE4. These data imply that apoE3 and apoE2 isoforms bind more tightly to Aβ than apoE4 and may thus facilitate the Aβ-apoE complex internalization via apoE receptors. Since apoE4 has only weak binding to Aβ, more Aβ would remain in the extracellular space and could activate microglia or directly damage neurons [7]. In another study, Ma and colleagues reported that when incubated with all three apoE isoforms, apoE4 caused the highest aggregation of Aβ1–42 [35]. This result supports our hypothesis that if Aβ aggregates more easily in the presence of apoE4, it may become inaccessible for internalization. In contrast with the previous two studies, Chan et al. found no difference in the binding of Aβ to apoE, regardless of apoE isoform or Aβ length, i.e. 40 versus 42 amino acids [9]. ApoE plays multiple roles in AD in addition to its binding to Aβ. These include its crucial role in cholesterol and lipid transport, neuronal repair and inflammation. For review see [36,43,48].

Understanding the contribution of ACT to AD pathogenesis is important because ACT is an acute phase protein upregulated by cytokines during inflammation. Since anti-inflammatory drugs are being considered as a potential remedy alone, or part of a cocktail with β- and γ-secretase inhibitors and, perhaps, Aβ immunization, it is imperative to evaluate the effect of the anti-inflammatory drugs on ACT and Aβ persistence in the brain. Recently, it has been shown that ibuprofen suppresses the production of IL-1, GFAP, plaque pathology and inflammation in a mouse model for AD [30]. It remains to be determined whether the levels of mouse ACT or apoE are also reduced and whether this reduction may have a detrimental effect on neuronal repair.

1.5. Animal models to study the effects of ACT in plaque formation

In order to understand the contribution of ACT to plaque formation and to Aβ deposition and neurotoxicity we

crossed the plaque-producing PDGF-APP mice with a transgenic mouse producing human ACT in astrocytes (APP/ACT mice). The ACT expression was driven by the GFAP promoter. Upon neuropathological examination of the area occupied by plaques, the APP/ACT mice had a two fold larger area of brain occupied by plaques at 7, 14 and 20 months when compared to APP mice [1,40]. Our findings of the increased plaque load in the APP/ACT compared to those of APP mice have been recently confirmed [41]. These studies suggest that increased expression of ACT promotes Aβ deposition.

To our surprise, the percentage area occupied by presynaptic terminals immunolabelled by antibodies against synaptophysin and GAP-43, another synaptic marker, was unchanged compared with those values for APP singly transgenic mice but significantly lower than those for control mice [40]. Thus, having twice as many plaques containing fibrillar Aβ did not induce more synaptic toxicity than that present in APP mice, again suggesting that the culprit may be the soluble oligomeric Aβ and not the fibrillar Aβ. Unfortunately, the conversion of Aβ from soluble monomeric to oligomeric to protofibrillar and fibrillar is rapid, especially with Aβ42. At this time we lack the tools to correlate a certain Aβ structure with its bioactivity or neurotoxicity. It would be interesting to compare the conversion of soluble Aβ into fibrils in the absence and presence of ACT by atomic force microscopy. In *in vitro* experiments Aβ has been shown to exist as a mixture of all forms depending on the buffer, salt conditions, and length of incubation.

In our earlier cell culture studies on Aβ degradation we observed that when we incubated conditioned medium containing Aβ-degrading activity with several serine protease inhibitors, the activity was inhibited. ACT also inhibited Aβ degradation [54]. These results suggested that ACT may either directly inhibit an Aβ-degrading protease or that it may bind to Aβ rendering it protease-resistant. In a recent study we preincubated conditioned medium with ACT in order to inhibit a protease that may degrade Aβ, and then added Aβ to the incubation mixture. There was no inhibition of Aβ degradation. Conversely, when we preincubated Aβ with ACT allowing these two molecules to bind each other, and then added the proteolytically active conditioned medium, Aβ degradation did not occur (Gaidos and Abraham, unpublished results). These data suggest that once Aβ binds to ACT, Aβ becomes resistant to degradation. Together with the in vivo data obtained from the APP/ACT mice, we conclude that ACT binds to newly formed Aβ and prevents its further degradation by proteases or its clearance via internalization by receptor mediated endocytosis. This way ACT may promote extracellular Aβ accumulation.

1.6. Future directions

Two important discoveries related to AD occurred in the 1980s. First, the seminal discovery by Glenner of the primary sequence of the first 28 amino acids of Aβ [20]. Based on the Aβ sequence, APP was cloned, and mutations in APP that cause familial AD have been detected. Second, inflammation-related proteins were detected in the AD brain, including proteins associated with the Aβ plaques. Among them are the complement factors [15], ACT [2], and IL-1β [21]. Despite the wealth of knowledge on Aβ biology and on inflammation, much work is still needed to understand the pathophysiology of neurodegeneration in AD.

The main questions that need to be addressed are:

1. Does Aβ cause neurodegeneration that leads to cognitive impairment? The present clinical studies using agents aimed at reducing the Aβ load such as secretase inhibitors and Aβ vaccines should answer this crucial question in the next few years. Will the "Amyloid hypothesis" survive the scrutiny of human studies?
2. If Aβ is toxic, which form is more toxic, the soluble or the fibrillar? Or is the toxicity cell type specific?
3. Does the toxicity result from the intracellular or extracellular Aβ?
4. What starts the vicious cycle of neurodegeneration? At which step should we intervene?
5. Does the inflammation exacerbate the neurodegeneration? Prevention studies with anti-inflammatory drugs in cognitively healthy individuals 70 years old or older with one first degree relative with AD have just started.
6. Is the activation of astrocytes and microglia beneficial in any way during the disease? If it is, will anti-inflammatory agents prove to be counter productive?

Judging from the major findings of the last twenty years, the next years should bring a deeper understanding of what causes AD and how it can be treated.

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