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Interactions of β -Amyloid Peptide with Fibrinogen and Coagulation Factor XII may contribute to Alzheimer's Disease

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Abstract

Purpose of the Review—To review the evidence that the Alzheimer peptide β -amyloid ($A\beta$) interacts with the blood coagulation system and influences the pathophysiology of the disease.

Recent findings—That $A\beta$ can interact with fibrinogen and blood coagulation Factor XII and trigger ischemia and inflammation.

Summary— $A\beta$ interacts with fibrinogen and FXII. These interactions can lead to increased clotting, abnormal clot formation, persistent fibrin deposition, and generation of pro-inflammatory molecules. These events can damage neurons and could contribute to the cognitive decline in Alzheimer's disease patients.

Keywords

Alzheimer's disease; β -amyloid peptide; fibrinogen; Factor XII

Introduction

Alzheimer's disease (AD) leads to cognitive impairment and is eventually fatal. The cognitive decline is associated with extensive neuronal degeneration. The most well-known pathological features of AD are extracellular $A\beta$ plaques, intracellular tau tangles, neuroinflammation, and neuronal loss. Less discussed is that AD is often associated with cerebrovascular abnormalities [1]. Recently, the vasculature of 2083 AD postmortem samples were analyzed, and the conclusion was “concurrent vascular disease strongly correlates with cognitive dysfunction” in AD [2]. The symptoms of AD and cerebrovascular pathology could be independent co-morbidities, with both being increased in aging populations. However, it is also possible that there is a mechanistic link between AD and vascular pathology.

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If AD and vascular pathology are connected, what are the mechanistic links?

While the mechanisms behind neuronal dysfunction and cognitive decline in AD are heterogeneous and complex, abundant evidence points to accumulation of A β as one cause of AD. A β is generated when amyloid- β precursor protein (APP) is cleaved by β - and γ -secretases. Although the primary physiological function of APP is still unclear, it can participate in neurogenesis, synapse formation, and cell adhesion [3, 4]. Once liberated from APP on the cell surface, A β is released into the extracellular space and can form aggregation-prone oligomers, protofibrils, and fibrils in the brain parenchyma. Normally, the generation of A β in the brain is balanced by its clearance, and its accumulation in AD is thought to be the result of progressively impaired or overwhelmed clearance mechanisms. As A β is cleared from the brain, it can access extracellular fluids like cerebrospinal fluid (CSF) and blood [5], which would bring it in contact with plasma proteins. Since much of the A β produced in the brain is cleared through the cerebral vasculature, A β levels are higher in CNS venous blood compared to arterial blood [6] with some studies showing that elevated plasma A β levels are an early event in AD development [7, 8]. During clearance, A β can also accumulate around blood vessels as cerebral amyloid angiopathy (CAA).

A possible role of A β -fibrinogen interaction in AD

AD patients show increased fibrin deposition in the brain, including areas associated with cell death [9–13], suggesting that fibrin accumulation may contribute to neurodegeneration in AD. This idea is supported by work in AD mice. Similar to AD patients, AD mice have increased fibrin deposition in their brains, with fibrin co-localizing with dystrophic neurites [9, 10, 14]. Pharmacological or genetic reduction of circulating fibrinogen in AD mice reduces fibrin deposition in the brain and improves their cognitive performance [10], indicating that fibrin deposition participates in the development and/or progression of AD in this model. Furthermore, fibrinogen-derived peptides are also increased in the plasma and CSF of AD patients [15–17], indicating that fibrinogen or fibrinogen-derived peptides could be potential biomarkers for diagnosis in some AD patients.

The inflammatory properties of fibrin together with its potential role in CNS signal transduction provide a possible mechanistic link between fibrin deposition in the brain, neuroinflammation, and neuronal dysfunction [18, 19]. In addition to its pathological effects in the brain parenchyma, persistent fibrin within blood vessel walls and in the vessel lumen can also contribute to AD pathology. Fibrin clots can occlude capillaries and restrict blood flow, leading to microinfarcts and damage to downstream cells.

In AD, fibrin(ogen) deposition may be precipitated and/or exacerbated by its interaction with A β [20–22], which has been investigated using electron microscopy, X-ray crystallography, and other *in vitro* techniques. A β specifically interacts with fibrinogen with a K_d of 26.3 ± 6.7 nM and also binds to pre-formed fibrin fibrils [20, 21]. A β -fibrin(ogen) binding is mediated by the central region of A β and by two regions on fibrin(ogen), the C-terminus of the β -chain and the α C region of the α -chain [20–22]. Binding of A β to fibrinogen has functional consequences: it induces a structural change in the C-terminal

region of the fibrinogen β -chain (β 384–393) [22], precipitates fibrinogen oligomerization [20], and results in the formation of fibrin with increased resistance to fibrinolysis [10, 21]. A β delays fibrinolysis via two mechanisms: 1) by inducing a tighter fibrin network composed of thinner fibers; and 2) by inhibiting the plasmin(ogen)-fibrin interaction [21], likely through steric interference with plasminogen's binding sites on fibrin A α residues 148–160 and on the α C region of fibrin, which are in close spatial proximity to the β -chain and α C binding sites of A β , respectively. Another consequence of A β binding to the α C region of fibrinogen and blocking plasmin-mediated cleavage at this site is the generation of increased levels of a plasmin-resistant fibrin degradation fragment [22], which if found in AD patients, could serve as a possible marker of fibrin(ogen)-related AD pathology.

In the brain parenchyma, extravasated fibrin(ogen) could come in contact with high concentrations of soluble A β released from neurons and with soluble A β surrounding A β plaques. In the vessel wall, fibrinogen may interact with increased levels of soluble A β near CAA deposits [23, 24]. Thus, the interaction between A β and fibrinogen in the brain parenchyma and/or vessels may result in the formation of abnormal, persistent fibrin and in its deposition along cerebrovascular walls. Over time, this could lead to microinfarcts with subsequent hemorrhage, inflammation and blood-brain barrier disruption, all pathologies commonly observed in AD.

A β has been shown to interact with numerous other circulating components including erythrocytes [25, 26], tissue plasminogen activator [27], apolipoprotein E [28], apolipoprotein J [29], α 2-macroglobulin [30], albumin [31], and members of the classical and alternative complement cascades [32, 33]. These interactions between A β and mediators of coagulation and inflammation could predispose blood to clotting. Indeed, there is evidence that circulating A β can elicit a clinically meaningful prothrombotic state, since plasma A β levels are correlated with infarctions as determined by MRI [34]. This prothrombotic state might be manifest in areas most sensitive to circulatory deficits, such as the hippocampus [35], providing one mechanism by which circulating A β could contribute to initiation of neurodegeneration in that region. At the same time, these interactions could contribute to the development of a systemic proinflammatory state. The idea that peripheral inflammation may contribute to neuropathology in AD is supported by studies demonstrating that peripheral markers of inflammation increase the risk of AD, that incidence of systemic infections increase the risk of dementia, and that cognitive impairment in AD is exacerbated during and after systemic infection [36–38]. Thus, activation and/or modulation of the delicately balanced coagulation and inflammatory systems by A β could lead to minor but chronic and pathological occlusion and inflammation, both of which could contribute to the neuronal death observed in AD.

The FXII contact system is significant in AD pathophysiology in humans and mouse models

A β also binds to and activates coagulation factor XII (FXII), which can then initiate the contact system [39–43], a proteolytic cascade that leads both to clot formation through the intrinsic coagulation pathway and also to inflammation via bradykinin release after high

molecular weight kininogen (HK) cleavage. A β -mediated activation of FXII could be one mechanism behind the increased contact system activation observed in the plasma and CSF of AD patients and mouse models [39, 40]

The contact system can initiate vascular pathology and inflammation, both of which are implicated in AD. Thus, this system could contribute to these pathologies in AD. Connections between FXII and AD have been reported: A β plaques contain FXII [44], the AD brain parenchyma exhibits higher plasma kallikrein activity [45], and AD patients have increased HK cleavage in their CSF [46]. In addition, AD patients and mice have higher plasma levels of activated FXII (FXIIa) and increased HK cleavage compared to controls [39].

To determine if FXII is causally related to AD, plasma FXII was depleted in AD mice using antisense oligonucleotide (ASO)-mediated messenger RNA knockdown. This depletion inhibited HK cleavage in plasma and reduced neuroinflammation, fibrin(ogen) deposition, and neuronal degeneration in the brain. The improved brain pathology was accompanied by better cognitive function [47]. These results provide a mechanistic link between A β and the contact system with resulting neuroinflammation, neuronal degeneration, and cognitive impairment.

There is no effective treatment for AD. However, a link between FXII activation and the pathogenesis of AD provides a possible novel approach to treatment. The contact system is an attractive target for therapy [48]. Humans deficient in FXII and mice with knockout of the FXII, FXI, or HK gene all have normal hemostasis. Deficiencies in the contact system protect mice from thrombogenic challenges such as clotting after arterial injury and experimental cerebral ischemia [49, 50].

Since preventing FXII activation attenuates AD pathology in a mouse model [47], therapies designed to block the contact system might slow disease progression while not affecting normal hemostasis. In addition, this approach would block bradykinin release from HK and thereby reduce inflammation in this disease. Thus, the contact system might represent new targets to suppress both thrombotic and inflammatory contributions to AD progression. Positive results might be able to be applied to AD patients rapidly. For example, a small molecule inhibitor of PK, ecallantide, is currently approved for treatment of hereditary angioedema [51]. An antibody inhibitor of PK [52] has also been developed, which is slated for a phase 3 trial and possible FDA approval by 2018. Some of these reagents might be useful for the treatment of AD in the future.

Conclusion

The data reviewed here suggest that the interaction of A β with fibrin(ogen) can lead to increased fibrin deposition in cerebral blood vessels, and that these accumulated fibrin deposits may disrupt cerebral blood flow and induce microinfarcts, inflammation, and BBB damage, all of which are aspects of cerebrovascular dysfunction observed in AD. At the same time, A β 's ability to activate FXII may contribute to increased fibrin generation through the intrinsic coagulation pathway as well as to increased inflammation and vascular

permeability through bradykinin release from HK. These possible roles of A β in thrombosis, fibrinolysis, and inflammation via its interaction with fibrinogen and FXII are summarized in Figure 1.

Combination therapy has been indispensable in making therapeutic breakthroughs in other complex diseases like cancer and AIDS. AD is an extremely complex disease with many probable pathogenic mechanisms, and treatment will likely involve combination therapy targeting various aspects of the pathological network [53]. The interactions of A β with fibrinogen and FXII described here are possible components of this network. If these mechanisms are involved in AD pathophysiology, targeted therapy could be designed for AD patients identified as having circulatory abnormalities stemming from A β 's interaction with these blood components. Given the heterogeneity of this disease, targeting a combination of different pathogenic pathways in different individuals will likely be a valuable approach to treatment.

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Key Points

- A β can interact with fibrinogen leading to structurally abnormal, persistent blood clots
- A β can interact with FXII leading to increased clotting and release of the pro-inflammatory peptide bradykinin
- The interaction of A β with fibrinogen and/or FXII could participate in Alzheimer's disease pathophysiology

Figure 1.

Proposed model for the role of A β in thrombosis, fibrinolysis, and inflammation via its interaction with fibrinogen and FXII. FXII activation by A β may induce inflammation through bradykinin activation and increase fibrin generation through the intrinsic coagulation pathway. Furthermore, the interaction of A β with fibrin(ogen) can decrease fibrinolysis via abnormal fibrin clot formation as well as by inhibiting the plasmin(ogen)-fibrin interaction. Together, these processes may increase the level of fibrin and inflammation in the cerebral blood vessels, which could induce or enhance the cerebrovascular dysfunction observed in AD patients.