

INVITED REVIEW

Fibrinogen, a possible key player in Alzheimer's disease

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Summary. Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive loss of cognitive function and subsequent death. Since the first case of this disease was diagnosed one century ago, much effort has been dedicated to find a cure. However, even though progress has been made in the knowledge of the pathogenesis of this disease, an effective treatment has not been found. Therefore, new approaches are needed urgently. AD patients have an abnormal cerebral vasculature and brain hypoperfusion, and a large body of research, including some from our lab, implicates cerebrovascular dysfunction as a contributing factor to AD. Reducing fibrinogen, a circulating protein critical in hemostasis, provides a significant decrease in the neurovascular damage, blood–brain barrier permeability and neuroinflammation present in AD. These studies implicate fibrinogen as a possible contributor to AD.

Keywords: Alzheimer's disease, blood–brain barrier, fibrinogen, neurovascular damage.

Introduction

AD is the leading cause of dementia in the elderly with approximately 18 million people affected worldwide. This number is increasing due to an aging population. The early symptoms of AD, memory loss and general cognitive decline, are due to loss of neurons in the hippocampus and cortex. Despite the two-well established and classical diagnostic features of AD, the extracellular neuritic plaques and the intracellular neurofibrillary tangles [1], the precise cause of neuronal death is not known. Although progress has been made in the molecular and cellular understanding of the pathogenesis of AD [2,3], numerous clinical trials have failed [4] and there are only five drugs approved which have minor effects on disease progression [5]. This lack of an effective treatment for AD has promoted the search of other theories besides brain deposition of amyloid as the main cause of this neurodegenerative disease. There is significant evidence that AD patients suffer from inadequate circulation and cerebro-

vascular pathology, and one theory that is gaining evidence is the importance of vascular factors in the onset and progression of this disease [6–8].

Amyloid hypothesis

The extracellular plaques in the AD brain are composed primarily of a 40–42 amino acid peptide called the amyloid- β peptide (A β) that is proteolytically derived from the amyloid- β precursor protein (APP). The A β peptide is normally soluble, but it can aggregate depositing as plaques in the brain parenchyma and as cerebral amyloid angiopathy (CAA) in the blood vessels [9]. There is substantial evidence that A β is involved in the pathology of AD [10]. For example, all of the rare human mutations that lead to early onset familial AD involve mutations that lead to increased expression of APP or increased generation or fibrillization of A β via the γ -secretase pathway. Transgenic mice that over-express human APP develop A β plaques, inflammation, and cognitive deficiencies [11–13]. Although A β is clearly implicated in AD, it is not understood how this peptide induces neuronal death or cognitive deficits. Different AD animal models have been immunized against A β and a cognitive improvement has been detected, even in the absence of a decrease in the A β load [14]. Numerous clinical trials in humans are in progress [15], but the first one of immunization against A β failed [16]. In addition, the extracellular amyloid plaques do not correlate well with severity of dementia, and it is likely that oligomers, the small precursor of these insoluble deposits, have a principal role perturbing some other brain property [17].

Vascular disease in AD

Cerebrovascular dysfunction

The cerebrovascular structure and function in the AD brain are damaged and the brain is especially susceptible to interruptions in blood flow as it has a high demand for oxygen and glucose and almost no long-term energy stores [6]. A decrease in cerebral blood flow has been reported in AD patients and, furthermore, a correlation between the level of cerebral hypoperfusion and the degree of dementia has been identified [6]. Besides the cortical and leptomeningeal vessels affected by the deposition of A β as CAA (see below), the

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microvasculature also presents abnormalities that include irregular shape, degeneration and atrophy of the smooth muscle cells, pericytes and endothelial cells as well as swollen glial end feet [6]. All these affected structures are part of the neurovascular unit, a structure composed by neurons, astrocytes and vascular cells which functions in maintenance of brain hemostasis and the defense against brain injury [7,18]. Consistent with these findings, studies of AD mice show early endothelial cell dysfunction, which reduces their response to vasodilators [19] and impairs critical regulation of blood flow [20,21]. Blood microvessels isolated from AD patients have been shown to be directly toxic to cultured neurons [22]. Examination of AD brains reveals white matter lesions resembling those observed after ischemia [23], and compromised blood flow can lead to the pathological synaptic changes characteristic of AD [6,24]. All these studies suggest that some of the neuronal loss in AD could be secondary to circulatory deficiencies [6,8,25].

Epidemiological studies

In addition to the profound cerebrovascular dysfunction presented in AD brain, epidemiological studies link vascular disease with AD [26]. Cardiovascular disease is associated with more rapid cognitive decline in AD patients [27] and indicators or risk factors for vascular disease such as atherosclerosis [28,29], stroke [30,31], heart disease [31] and atrial fibrillation [27,28], among others, correlate well with disease pathology in AD. More than twenty vascular-related factors that provoke a decrease in cerebral perfusion have been identified as risk factors for AD [32] and an increased number of vascular risk factors are related to a higher probability of suffering AD [30,33].

A β and abnormal hemostasis

Apart from all these studies supporting the idea of an important vascular contribution to AD, the deposition of A β in the vessels forming CAA may act as a decisive factor to the severity of the vascular pathology. CAA not only thickens the wall of the vessels, contributing to the disturbance in the blood flow [6] but also affects and promotes the degeneration of the cells of the vascular wall as well as promotes inflammation [34]. CAA correlates strongly with the severity of dementia and may play an important role in the pathogenesis of this disease [35]. Also, A β may affect the blood directly as it can augment blood platelet aggregation *in vitro* and increase thrombosis [36,37]. This result is supported by the observed protective effect of anti-platelet therapy against AD disease progression [38,39]. In fact, abnormal hemostasis in this disorder is suggested by elevated levels in AD patients of molecules such as plasminogen activator inhibitor (PAI-1) [40], von Willebrand factor [40,41], fibrin degradation products [41] and thrombin [42]. Interestingly, patients with atrial fibrillation and with a consequent increase in the prothrombotic state, present a significant increase in the risk of

developing AD [27,28] and furthermore, those patients treated with anticoagulants present less dementia and cognitive impairment [43]. These data also indicate the importance of the control of the hemostasis in AD.

Fibrinogen in AD

Fibrin is the primary protein component of a blood clot. Its inactive precursor, fibrinogen, circulates in the blood as a large complex molecule of 340 kDa [44]. Under normal circumstances, fibrinogen is excluded from the brain by the blood-brain barrier (BBB). However, the cerebrovascular pathology that takes place in the AD brain may affect the proper function of the BBB that tightly controls the communication between the circulation and the central nervous system and protects the brain's microenvironment from macromolecules in circulation [18]. BBB damage has been reported in AD transgenic mice [45-47] as well as in human AD patients [48-50] and fibrinogen gains access to the brain parenchyma and accumulates over time as AD pathology progresses [47,51,52]. Also, an increase in fibrinogen levels has been reported to be associated with risk for dementia and AD [53-55]. In addition, the plasmin/tissue plasminogen activator (tPA) system is affected in AD as proteolytic activity of plasmin is decreased in the AD brain [56] and, PAI-1, one of the inhibitors of tPA, is up-regulated in AD mice [57] and in the cerebrospinal fluid of AD patients [58]. With increased permeability of the BBB and diminished activity of fibrinolysis pathway components, the AD brain presents a situation that tends to accumulate fibrin. As fibrin(ogen) accumulation causes damage when present in the extravascular space [59], and induces pathology in the nervous system [60], the role of fibrin(ogen) deposition in AD needs further study.

An effective method to study the role of fibrinogen deposition in the cerebrovascular dysfunction in AD is by using two complementary approaches: genetic and pharmacologic modulation of fibrinogen and plasminogen levels in AD mice. For decreasing the fibrinogen levels, AD mice (TgCRND8, [13]) were crossed with fibrinogen-deficient mice [61]. Once mice that carried only one fibrinogen gene were generated, neurovascular damage and BBB permeability were compared with their AD littermates by measuring the degree of Evans Blue dye extravasation. AD mice with only one fibrinogen gene had a significant decrease in Evans blue extravasation compared to AD littermates indicating that the decrease in fibrinogen in these mice lessens pathology in the cortex and hippocampus (Fig. 1) [47]. To reduce circulating levels of fibrinogen pharmacologically, we treated AD mice with the fibrinogen inhibitor anicrod, a thrombin-like protease derived from the venom of the Malayan pit viper *Agkistrodon rhodostoma* (Fig. 1). This protease cleaves fibrinogen releasing fibrinopeptide A but not B and therefore prevents fibrinogen polymerization and crosslinking and allows its degradation and removal [62,63]. The treatment with anicrod provokes a reduction in

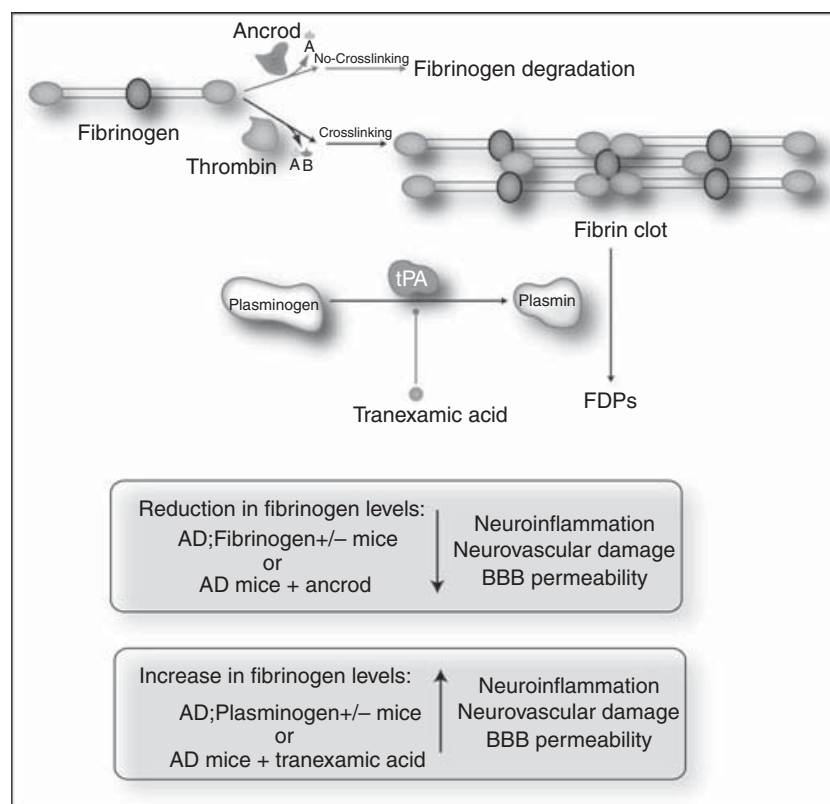


Fig. 1. Schematic representation of the pathways leading to fibrin formation and degradation. When fibrinogen is cleaved by the protease thrombin, the fibrinopeptides A and B are released and the fibrinogen dimers non-covalently polymerize to form protofibrils, which then undergo crosslinking and branch to form an insoluble network of fibrils or a 'fibrin clot'. This clot network incorporates platelets to functionally impede blood flow and arrest hemorrhage at sites of vascular injury. Fibrin is naturally degraded by plasmin, which is generated from plasminogen after it is cleaved by tPA. Modulation of fibrinogen levels by using anicrod to decrease the levels of fibrinogen in the blood or tranexamic acid to specifically block conversion of plasminogen into plasmin, influences the degree of pathology in AD. FDPs, fibrin degradation products. Representation of the fibrinogen molecule adapted from ref. [44].

fibrinogen levels by 50–75% in the mouse circulation [47] and this fibrinogen depletion in AD mice was accompanied by an improvement in the vascularization, a significant reduction in BBB permeability and an important decrease in microgliosis when compared with saline-treated mice [47].

We hypothesized that the reduction of plasmin activity in AD should have effects opposite to that of reduction in fibrinogen levels and would promote neurovascular pathology. For modulating the plasminogen levels in AD, plasminogen deficient mice [64,65] were crossed with AD mice. The loss of one plasminogen allele in AD mice produced a significant increase in Evans blue extravasation, indicating an exacerbation in the neurovascular pathology in the cortex and hippocampus [47]. When working with congenital knockout mice, there is always the possibility of developmental defects. Therefore and as previously done with the studies reducing fibrinogen in AD mice, we also targeted plasminogen using a pharmacologic approach to complement our genetic analyses. To disrupt fibrinolysis pharmacologically, we treated AD mice with the plasmin inhibitor, tranexamic acid (Fig. 1). Suppressing plasmin activity using this method led to an expected increase in fibrin deposition in the brain of AD mice compared with saline-treated AD mice and these elevated levels in fibrin were accompanied by an

increase in inflammation, neurovascular damage and BBB permeability [47].

Conclusion

Alzheimer's disease is a complex neurodegenerative disorder that has a strong vascular component in its pathology. Leakage of fibrinogen into the AD mouse brain is abnormal and aggravates the AD pathology. The relationship between fibrin(ogen) and A β is under investigation and this molecule could play an important role in the progression of this disease.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

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