Amyloid Beta and the Cerebral Vasculature

Paula Grammas

1. INTRODUCTION

The vascular pattern of amyloid beta (Aβ) deposition in the brain is commonly referred to as cerebral amyloid angiopathy (CAA) (1). CAA is an important cause of cerebral hemorrhages and may lead to ischemic infarction and dementia (2). A pure form of CAA, without parenchymal lesions, has been documented in hereditary cerebral hemorrhage, Dutch type, sporadic idiopathic CAA and in cerebrovascular malformations (3–5). Cerebrovascular amyloid deposition is associated with aging, and CAA is an important feature of several disorders associated with mutations in the amyloid precursor protein (APP) gene, as well as in Down's syndrome and Alzheimer's disease (AD) (6–8). Indeed, CAA is a key pathologic finding in 80–90% of AD cases (9,10). A recent study of 201 autopsy cases of elderly Japanese shows that the incidence and severity of CAA are significantly higher in AD cases compared to non-AD cases (11). Also, some genetic risk factors associated with the AD are involved in the pathogenesis of CAA, including apolipoprotein E (apoE) genotype, presenilin 1, and α₁-antichymotrypsin (12–14).

The genetic factors that regulate Aβ deposition in the vasculature have not been defined. A study examining the relationship between apo E genotype and the relative extent of Aβ accumulation in the brain demonstrates that expression of apo Eε4 leads to a higher level of Aβ in the vasculature compared to Aβ levels in the brain parenchyma (15). In addition, the severity of CAA among apo Eε4 carriers is significantly higher than among non-ε4 carriers (11). The Dutch, Flemish, Italian, and Arctic mutations in the APP gene that render Aβ resistant to proteolysis by neprilysin, a peptidase important for the catabolism of Aβ in the brain, are associated with CAA (16). Also, Yamada and colleagues (17) demonstrate an association between a polymorphism of the gene encoding for neprilysin and an increased risk of CAA. It is likely that multiple mechanisms contribute to the deposition of Aβ in brain blood vessel walls, including endogenous vascular synthesis, blood-to-brain transport, and impaired clearance of brain Aβ.

2. MECHANISMS OF VASCULAR Aβ DEPOSITION

The events and/or processes that regulate Aβ availability in the cerebral vasculature, systemic circulation, and the brain could contribute to the deposition of vascular Aβ observed in CAA and AD.

2.1. Endogenous Vascular Synthesis of Aβ

APP mRNA is expressed throughout cerebral vessel walls. The demonstration of APP-mRNA at all vascular sites where amyloid formation occurs supports an important contribution for locally derived Aβ to cerebrovascular amyloidosis (18). The notion that Aβ deposition in AD results from
vascular production of Aβ is supported by data showing that proteins elevated in the AD brain, specifically in AD blood vessels, increase secretion and/or expression of APP in endothelial cells. For example, thrombin, a multifunctional coagulant and inflammatory mediator, has been detected in both brain vessel walls and senile plaques in AD (19,20). This protease, via activation of cell surface thrombin receptors, induces APP secretion from endothelial cells (21). The inflammatory cytokine interleukin (IL)-1 also upregulates APP gene expression in endothelial cells (22). A causal role for IL-1 in vascular Aβ deposition in AD is supported by the author’s data showing that isolated brain microvessels from patients with AD express high levels of several inflammatory cytokines, including IL-1 (23). The presence in the vessel wall of both APP mRNA and high levels of proteins that regulate APP expression in endothelial cells implicate the vasculature as a source of vascular Aβ in AD.

2.2. Transport of Aβ Across the Blood–Brain Barrier

Increased transport of circulating Aβ across the blood–brain barrier (BBB) is also a potential mechanism for exacerbating cerebral amyloidosis (24–26). The idea that vascular Aβ derives from blood borne Aβ is supported by studies demonstrating specific mechanisms for brain capillary sequestration and BBB transport of 125I-Aβ1–40 synthetic peptide and its complexes with apolipoprotein J and apoE4 (24,27,28). It has been suggested that the receptor for advanced glycation end products (RAGE) on the brain vascular endothelium facilitates influx of Aβ into the brain from the systemic circulation (25,29). The possibility that this RAGE-mediated transport contributes to elevated levels of Aβ in the brain and vasculature in AD is supported by data showing elevated expression of RAGE in cells of Aβ containing vessels (30).

Another potential factor that can influence blood to brain transport of Aβ and is pathogenically relevant in AD is aging. Indeed, aging is the most important risk for the development of AD. In a study using an intravenous injection of labeled Aβ, Zlokovic and colleagues (31) show that compared to adult animals, aged squirrel monkeys show increased transendothelial transport of blood-borne Aβ1–40, as well as increased microvascular Aβ accumulation. Similarly, in a more recent study, this group demonstrates enhanced cerebrovascular sequestration of blood-borne Aβ in aged nonhuman primates (32). Brain microvascular sequestration of Aβ is also found in rodents (33,34).

2.3. Impaired Clearance of Brain Aβ

It has been suggested that cerebral amyloidosis in sporadic AD is a “storage” disease caused by inefficient clearance of the peptide that is produced at normal levels (26). Both physical and biochemical abnormalities in brain blood vessels could contribute to vascular Aβ accumulation. For example, Aβ is eliminated from the extracellular spaces of the human brain by a perivascular route, draining along the walls of cortical arteries to leptomeningeal arteries (35). A study using serial sections shows that cortical arteries feeding capillary beds with Aβ angiopathy are occluded by thrombi, suggesting that Aβ normally eliminated from the brain along vascular pathways may become blocked in the AD or aged brain, resulting in CAA (36).

Biochemical mechanisms that govern elimination of Aβ peptide from the brain are poorly understood. Intracerebral microinjections of radioiodinated Aβ1–40 in young mice results in rapid clearance of the peptide, mainly by vascular transport across the BBB (37). This clearance is inhibited by antibodies against low-density lipoprotein receptor-related protein-1 (LRP-1) and α2-macroglobulin (26). LRP-1 is abundant in the brain microvessels of young mice and is downregulated in vessels from older animals. Also, clearance is significantly reduced in apoE knockout mice (37). The demonstration of a correlation between regional Aβ accumulation in brains of AD and downregulation of vascular LRP-1 supports its importance in AD (37). Also, using single photon emission computed tomography (SPECT) to assess elimination of Aβ peptide from the brains of squirrel monkeys, an age-dependent increase in Aβ deposition has been documented, suggesting that with age, impaired Aβ clearance across the BBB may contribute to the development of CAA (38).