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Review

Cerebrovascular requirement for sealant, anti-coagulant and remodeling molecules that allow for the maintenance of vascular integrity and blood supply

Craig S. Atwood[a,b,*], Richard L. Bowen[c], Mark A. Smith[b], George Perry[b]

[a]*School of Medicine, University of Wisconsin and William S. Middleton Memorial Veterans Administration, GRECC 11G, 2500 Overlook Terrace, Madison, WI 53705, USA*
[b]*Institute of Pathology, Case Western Reserve University, 2085 Adelbert Road, Cleveland, OH 44106, USA*
[c]*Voyager Pharmaceutical Corporation, 8450 Colonnade Center Drive, Suite 409, Raleigh, NC 27615, USA*

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Abstract

The integrity of the vasculature and the maintenance of the blood supply to the brain are crucial for the survival of higher vertebrates. However, peripheral mechanisms of sealing the vasculature that rely on the clotting of blood and platelet aggregation around the site of a 'leak' would lead to decreased cerebral perfusion and compromise the viability of terminally differentiated and irreplaceable neurons. Therefore, in higher organisms it is likely that a sealant/anti-coagulant system that maintains vascular supply has evolved as a necessity to life. We propose that one such system involves the amyloid-β precursor protein (AβPP) and its cleavage product Aβ since (1) both AβPP/Aβ are known to deposit in the media of the cerebrovasculature wall following localized injury, (2) Aβ is generated from AβPP, a known acute phase reactant, (3) Aβ's physiochemical properties allow it to span between the extracellular matrix and the (endothelial) cell membrane and under inflammatory conditions aggregate to form an intracranial 'scab', thereby maintaining structural integrity of the blood brain barrier, (4) AβPP/Aβ together act as an anti-coagulant, (5) Aβ promotes vascular/neuronal remodeling, and (6) Aβ deposits resolve after injury. These properties are consistent with the acute phase generation and rapid cortical deposition of AβPP/Aβ following injury (either sustained by trauma or stresses associated with aging) that would be an important compensatory response aimed at limiting the loss of terminally differentiated neurons. Such a system would allow the maintenance of blood supply to the brain by sealing vascular lesions, preventing hemorrhagic stroke while at the same time inhibiting the coagulation cascade from blocking capillaries. Obviously, strategies to remove Aβ would have serious consequences for the integrity of the blood–brain barrier. Indeed, recent in vivo evidence demonstrates that the removal of deposited Aβ from the vasculature leads to increased cerebral microhemorrhage and strongly support the above mentioned functions of AβPP/Aβ. These insights also explain the root cause of the encephalitis and meningitis suffered by individuals in immunotherapy trials as being directly associated with the removal of Aβ from the vasculature, i.e. immunological responses to Aβ vaccination do not discriminate between physiologically purposive deposits of Aβ (vascular deposits) and pathological deposits of Aβ (senile plaques).

Theme: Cellular and molecular biology

Topic: Blood–brain barrier

Keywords: Amyloid-β; Anti-coagulant; Blood–brain barrier; Blood supply; Cerebrovasculature; Hemorrhage; Sealant; Vascular integrity

Contents

*Corresponding author. Tel.: +1-608-256-1901, Ext. 11664; fax: +1-608-280-7248.
E-mail address: csa@medicine.wisc.edu (C.S. Atwood).

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1. Introduction

Nowhere in the body is the integrity of the vasculature (the blood–brain barrier (BBB)) and the maintenance of the blood supply more important than in the brain, both for maintaining its nourishment and in preventing hemorrhage that would compromise nutrient transfer into the brain. Since cerebrovascular hemorrhage has serious consequences for neuronal and organismal survival, it would seem likely that mechanisms to prevent and/or limit vascular rupture must have evolved, particularly in higher vertebrates of greater lifespan in which there is an increased time-related potential for vascular rupture. Indeed, it is difficult to understand how the integrity of such an extensive network that meanders more than *600 km* through the human brain [74] could be maintained without such a system (Fig. 1; [81]).

Sealant systems do of course exist in the periphery, with the coagulation cascade leading to the clotting of blood and platelet aggregation around the site of a 'leak', together with macrophage activation providing for a seal to prevent blood components entering the brain. An obvious question is why platelet-induced sealing of a wound, such as in the periphery, could not fulfill such a role in the vasculature of the brain? The brain unlike other tissues, has a limited ability to replace the largely terminally differentiated neurons. Thus, unlike the periphery, where vascular blockage and macrophage activation lead to the death of cells surrounding the lesion, such blockage would lead to ischemic stroke and substantive, permanent neuronal death in the brain. Any partial blockage of the vasculature that leads to decreased cerebral blood flow and the supply of the major brain fuels, glucose and oxygen, also would greatly compromise the functioning and viability of neighboring neurons. Clearance of such a blockage would then lead to neurodegeneration such as occurs with ischemic-reperfusion injury.

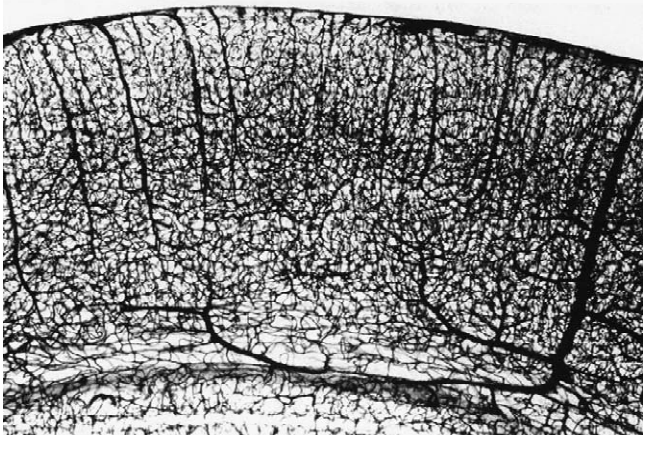

Fig. 1. Cerebrovascular network of the brain. India ink staining of the rat brain illustrates the extensive vascular network required to nourish the brain (from Ref. [12]), but also the requirement for an efficient vascular sealant system.

Normal clotting involves platelet-receptor glycoprotein Ibα (GPIbα) and immobilized von Willebrand factor (VWF) that mediate the rolling of platelets at sites of vascular damage [52]. Rolling reduces platelet velocity and prolongs the contact time with reactive components of the cell matrix which facilitates platelet activation and subsequent integrin-mediated firm attachment [114]. Exposure of VWF and collagen facilitate the adhesion of circulating platelets via GPIb-IX-V and integrin α2β1, respectively, to the damaged vessel wall. This process activates platelets and leads to a conformational change of a second integrin αIIbβ3 that facilitates fibrinogen binding and platelet aggregation. Thrombin generated at the blood–plaque interface converts fibrinogen to fibrin, which stabilizes thrombus growth. Given our argument that such a system may promote neurodegeneration, we predict that in the brain, unlike the periphery, there are decreased levels of VWF and GPIbα.

Although injury is well known to induce vascular

hemorrhage, changes in the cerebrovasculature with aging include decreased microvascular density, loss of endothelium, increased tortuosity, twisted/string vessels, fragmentation of the microvasculature, loss of the fine perivascular neural plexus and lumpy vessels. Such changes are far more pronounced in the neurodegenerative condition of Alzheimer's disease (AD) [25,97,27,61,19,88,86,63,13,38,53,54]. Cerebral capillary distortions caused by these changes create 'disturbed' rather than 'laminar' blood flow that impair normal delivery of essential nutrients to brain neurons as well as impede catabolic outflow of waste products [34]. Vascular changes also occur following ischemia [99], chronic hypoxia [46,14], chronic ethanol intoxication [68], chronic hypoperfusion [33], and behavioral treatments [122].

The following sections will focus, not on the causes of these age-related changes in vasculature (e.g. Ref. [25]), but rather how the brain responds to acute (head trauma) and chronic (aging, AD) stresses to prevent hemorrhage and maintain vascular blood supply.

2. Amyloid-β: a candidate vascular sealant, anticoagulant and remodeling molecule

With these thoughts in mind, it is likely that a mechanism has evolved to quickly seal any tear or rupture in the vasculature so as to limit damage associated with hemorrhage. Perhaps the best insights into identifying candidate neurovascular sealants come from studies of acute injury (i.e. head trauma, Fig. 2), known to significantly alter vascular structure and blood–brain barrier permeability (e.g. Ref. [87]). Acute phase molecules involved in the initiation, clearance and subsequent tissue rebuilding processes after acute injury [2,10] are prime candidates for such a function. The amyloid-β precursor protein (AβPP) is one such acute phase response protein [137,132,136,135,134], from which the Aβ protein is

Fig. 2. Head trauma induces cerebrovascular damage (rupture) and a sequence of biochemical changes that promote healing. These changes include Aβ deposition and its clearance during the healing process.

cleaved and rapidly deposits in a diffuse, non-congophilic manner, following head trauma [106,108,28,49]. The generation of Aβ from AβPP and its deposition following head injury strongly implicate Aβ in having a compensatory response to acute injury. Indeed, the rapid deposition of Aβ following trauma (within minutes) raises the question as to why this molecule would lay down so quickly, and what microenvironmental changes would induce its deposition ([9,7]; see Section 2.2).

Similar compensatory responses (Aβ deposition) might be expected with vascular compromise associated with aging and disease (i.e. AD, vascular dementia). Changes in vascular architecture with aging (described in the above section) would place additional (chronic) stress on the endothelium to maintain vascular integrity, and may explain such changes as amyloid deposition but also capillary basement thickening [86] and collagen type IV accumulation (fibrosis) [17]. It is perhaps not surprising that vascular amyloid deposition has been identified in virtually all AD patients and is indicative of age-related loss of vascular integrity in such stressed individuals [138].

2.1. Localization of Aβ deposition within the cerebrovasculature

That Aβ could operate as a sealant of the vasculature is of course suggested by its deposition within the tunica media of the cerebral vessel wall only within the brain (e.g. Refs. [110,85]) (Fig. 3). Histochemical and immunohistochemical analyses reveal the major component of vascular and perivascular Aβ deposits is Aβ1–40, while confocal laser scanning microscopy has demonstrated that Aβ1–40 deposits occur in and around blood vessels [85]. Such localization of diffuse amyloid to capillaries during times of vascular compromise, like that observed in head injury, AD, vascular dementia and stroke, strongly supports a role for Aβ in maintaining tight junctions. It could be visualized that Aβ forms a mesh or lattice that maintains the integrity of the endothelium and the BBB, detected as diffuse amyloid deposits following head injury [8]. Incomplete sealing, perhaps due to a breakdown in the systems generating or clearing Aβ, or during a major lesion that might result as we age, would result in vascular hemorrhage that presents as strokes and mini-strokes (hemorrhagic stroke, particularly in the elderly).

2.2. Physiochemical properties of Aβ are consistent with that required for a sealant molecule

A number of the physiochemical properties of Aβ support the idea that it acts as a vascular sealant [9,7]. Aβ is a small protein that aggregates under inflammatory conditions of mild acidosis and high metal ion concentrations, and contains both hydrophobic (C-terminus) and hydrophilic (N-terminus) regions that can span the plasma membrane and bind extracellular matrix (ECM) molecules [4,66,90]. Aβ has been shown to bind to heparan sulfate of the ECM (via residues 12–17 of the N-terminus, VHHQKL; [90,18,125]) (Fig. 4), and can therefore form a mesh between the basal lamina (containing heparan sulfate proteoglycan, laminin, and collagen IV) and endothelial cells to regulate adhesive events such as endothelium integrity, neurite outgrowth and synaptogenesis. Aβ deposits have been shown to be tightly anchored to the basal lamina since repeated washings of capillaries with 15% fail to detach them [110].

These properties make Aβ an excellent candidate molecule that could form an intracranial ‘scab’, thereby sealing or maintaining structural integrity. This ‘sealing reaction’ appears to be mediated by metal ions, particularly Zn and Cu, which have been shown to bind Aβ with high affinity both in vitro and ex vivo via histidine residues (6, 13 and 14) [4,6,35]. Metal ions and mildly acidotic conditions have been shown to induce Aβ aggregation [4,6,22,23,50], but not its fibrillization [149], in vitro. Indeed, recent evidence indicating that the insertion of Aβ into lipid bilayers is dependent upon Zn and Cu binding, pH and the cholesterol content of the membrane [31] indicates an important relationship between these molecules. The brain maintains high concentrations of both Cu (~70 μM) and Zn (~350 μM; [75]). Therefore, with the release of these metal ions during injury, Aβ could be rapidly assembled between the cell membrane and the extracellular space by Zn and/or Cu that are known to be mobilized to sites of injury and inflammation, and by the decrease in pH also known to be associated with injury and inflammation (reviewed in Refs. [4,5]). Therefore, metal ion and heparan binding to Aβ likely promote Aβ assembly at sites of damage (between the ECM and the cell membrane), while metal ion release would perhaps signal for the clearance of Aβ from membrane structures.

The binding and aggregation of Aβ is mediated by metal ion binding to histidine and tyrosine residues in the N-terminus [4,84] at concentrations expected to be present at sites of inflammation or injury [5]. The role of histidine residues in the aggregation (and ECM binding) of Aβ is supported by the fact that the loss of histidine residues, such as in rat Aβ which contains three amino acid substitutions (Arg→Gly, Tyr→Phe and His→Arg at positions 5, 10 and 13, respectively) [60] or following histidine modification, results in greatly diminished aggregation of Aβ by Cu(II), Zn(II) or Fe(III) [4,73]. These results indicate that histidine residues are essential for metal- and heparan-mediated assembly of Aβ between the membrane and extracellular space and may explain why cerebral Aβ deposition is not a feature of aged rats [60] even though soluble Aβ1–40 is produced by rat neuronal tissue [20]. Although the rodent form of Aβ does deposit in the rodent brain after traumatic brain injury, it is mainly detected within damaged axons [57,58], again suggesting that the

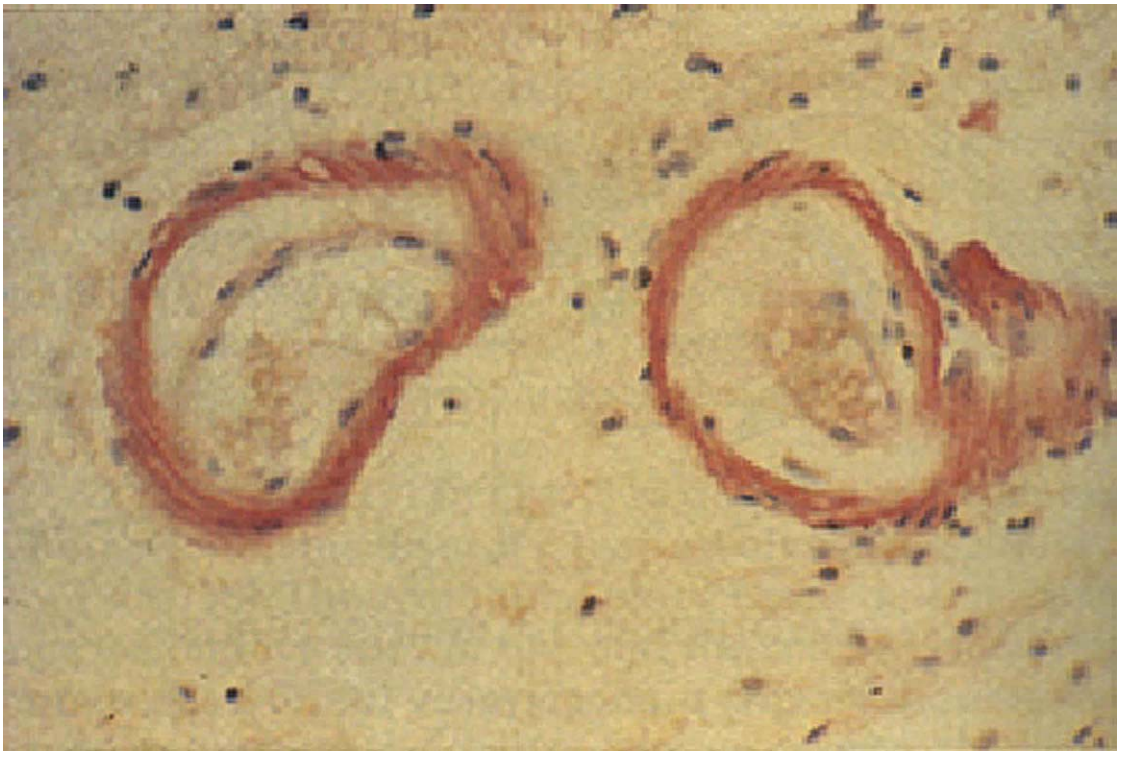

Fig. 3. Cerebrovascular amyloid deposition in the media of the vessel wall. Cross-section of a pair of cerebral arteries stained with Congo red (marked with arrows) showing characteristic amyloid-β deposition (Adapted from Ref. [65].

amino acid substitutions within the heparan proteoglycan binding site of Aβ may diminish binding to the ECM. This diminished binding of AβPP/Aβ may be less important in an animal that can successfully reproduce within a few months of life compared with an animal that must survive decades in order to successfully complete reproduction, i.e. the chances of brain trauma leading to compromised vascular supply are less likely to impact the ability of rodents as a species to survive compared to a long lived mammal. Long lived animals, and those that have a long period between birth and successfully raising young to reproductive age (e.g. bear, dog, rabbit, monkey, etc.), are those species that express the 'human' form of Aβ [60] and which deposits with aging. That AβPP knockout mice have no apparent pathology (and live in the protected environment of cages their whole life) is consistent with the idea that AβPP is required only during times of injury/degeneration.

We have previously shown that Aβ, unlike most proteins, binds Cu under acidotic conditions, in keeping with a role of Aβ as a molecule involved in maintaining structural integrity and/or as an antioxidant required under stress conditions [4,26]. In addition, and given the protein's redox properties, Aβ can dampen oxidative insults by binding excess or loosely bound redox active metal ions [123,115], which at the same time act to switch on its neurotrophic properties (antioxidant activity). We have proposed that the binding of Zn and Cu under these conditions produces aggregated Cu,Zn-Aβ that would serve as a superoxide-scavenging, solid-phase matrix, which disassembles when Zn and Cu levels lower as tissue damage resolves [101]. In this respect, we have found that the anti-oxidant activity of Aβ is modulated by Cu concentration [26]. Recently, the antioxidant properties of Aβ were confirmed by Kontush et al. [66], showing that Aβ prevents lipoprotein oxidation in cerebral spinal fluid (CSF), and by Zou et al. [151], who showed that monomeric Aβ1–40 inhibits the reduction of Fe(III) induced by vitamin C and the generation of $O_2^{-\cdot}$.

These properties of Aβ explain the acute phase generation and rapid cortical deposition of Aβ following head trauma [107], an important physiological response that would limit the loss of terminally differentiated neurons following head injury.

2.3. Aβ deposition prevents the coagulation cascade

Human cerebrovascular smooth muscle (HCSM) cell associated Aβ fibrils serve as a site for the tight binding of cell-secreted anticoagulant AβPP [133]. The increased secretion of secreted AβPP appears to be a response to Aβ deposition. AβPP is a potent inhibitor of key proteinases of the coagulation cascade, and so its enhanced localization on Aβ deposits provides a strong anticoagulant environment [132,136,119,118,79]. In addition, HCSM cell-surface Aβ fibrils are potent stimulators of tissue plasminogen

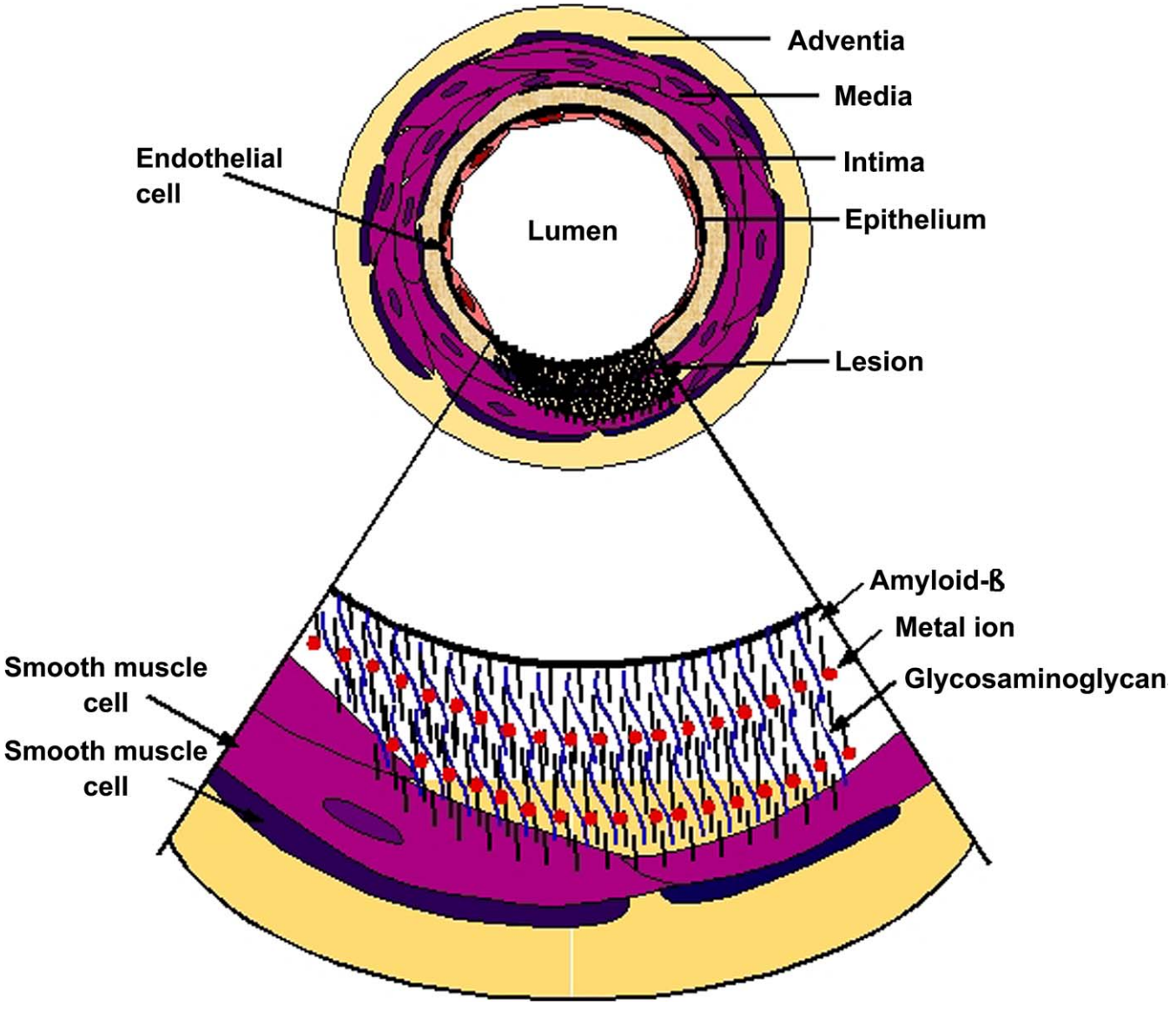

Fig. 4. Schematic diagram of early vascular lesion: Aβ binding to the extracellular components such as heparan sulfate proteoglycans allow for the sealing of vessels in order to prevent hemorrhage. The lesion is drawn from the epithelial layer, but also may arise from the basement membrane.

activator (tPA) creating a profibrinolytic milieu [64]. These findings indicate that Aβ fibril assembly on the HCSM cell surface results in both a strong anticoagulant and fibrinolytic environment. The modulation of the deposition versus the degradation of Aβ (e.g. by tPA, see below) will determine whether there is a loss of vessel wall integrity that could lead to hemorrhagic stroke.

2.4. Sources of Aβ for sealing

Sources of Aβ for sealing of vessels or maintenance of regional integrity include neurons, astrocytes, glia and/or vascular smooth muscle cells in close proximity to the lesion. AβPP is an acute phase reactant upregulated in response to inflammation and a multitude of associated degenerative cellular stresses (reviewed in [10]). Not only do stresses such as energy shortage and Ca(II) dysregulation promote AβPP expression, but they also route the metabolism of AβPP from the non-amyloidogenic to the amyloidogenic pathway. Inhibition of mitochondrial energy metabolism alters the processing of AβPP to generate amyloidogenic derivatives [44,80], while oxidative stress (likely associated with apoptosis) has been shown to increase the generation of Aβ [40,83,95]. Consistent with this response AβPP and Aβ have been detected in the human brain a couple of days after traumatic brain injury [107,94,45]. In addition, Emmerling et al. [104] found a sharp increase in the concentrations of Aβ1–40 and Aβ1–42, but not AβPP, in the CSF of individuals with severe traumatic brain injury. The release of Aβ into the CSF, together with other markers of traumatic brain injury indicates a neuronal source of Aβ

required during structural damage [104]. Evidence for a neuronal origin is further suggested by the fact that an AβPP23 transgenic mouse model of cerebral amyloid angiopathy (CAA) on an AβPP-null background develops a similar degree of both plaques and CAA, suggesting that a neuronal source of AβPP/Aβ is sufficient to induce cerebrovascular amyloid [24].

There also is evidence that Aβ may originate from vessels that contain CSM cells. Given the extensive network of vessels in the brain, it seems improbable that neuritic plaques are not associated with such vessels. It has been suggested that extensive deposition of Aβ, i.e. emboli, may lead to the degeneration and disappearance of the capillary, leaving cores of amyloid free in the parenchyma [110]. Thus, Aβ might originate primarily in the vascular tissue and either escape into the parenchyma from the Aβ-laden blood vessels or simply remain there after degeneration of the vessel to become cores of neuritic plaques. This is supported by the finding of increased levels of post-translational modifications in neuritic core Aβ1–42 compared with vascular Aβ1–42, indicating neuritic core Aβ is older than vascular Aβ1–42 [110]. Furthermore, the pattern of deposition of Aβ, perpendicular to the main axis of the vessel, appears to follow the pattern of the ECM associated with the smooth muscle cells of the arteriole, suggesting a vascular tissue source of Aβ at least in the larger arterioles [110].

Another source of Aβ may be directly from platelets and leukocytes in the bloodstream, which carry more than 90% of the circulating amyloid [21,32]. Reactive oxygen species (ROS) stimulate the tumbling and margination of platelets on the endothelium, mediated by P-selectin [41]. During degranulation of the platelets, Aβ could be released and deposited in walls of arterioles [132,119,21,117].

2.5. In vivo evidence for Aβ as a cerebrovascular sealant

Strong in vivo evidence that Aβ acts as a vascular sealant is shown by the fact that intravenous administration of tPA to a mouse model of CAA leads to an increase in microhemorrhages and can result in parenchymal and subarachnoidal hematomas [96,146]. In this vein, aggregated, but not nonaggregated Aβ increases the expression of mRNA encoding tPA and uPA [129]. Moreover, Aβ aggregates, in addition to fibrin aggregates and laminin, can activate tPA post-translationally [64,147,131] leading to the cleavage of plasminogen to the active protease plasmin [127,128]. This activity of Aβ is specific for tPA [147]. Importantly, a number of studies have shown that purified plasmin degrades Aβ at multiple sites and with a physiologically relevant efficiency, thereby blocking Aβ neurotoxicity in vitro [131,127,128,37]. Modulation of plasmin levels and activation would therefore dictate whether amyloid deposits or not. The conversion of diffuse amyloid deposits into fibrillar Aβ may mediate the activation of tPA and induce Aβ, and perhaps also laminin (and fibrin?) degradation/clearance, leading to a breakdown in the integrity of the vascular media and rupture of vessels. Which protease is responsible for Aβ degradation (i.e. plasmin, neprilysin, insulin-degrading enzyme, endothelin-converting enzyme, etc) is not clear (see below). Nonetheless, that removal of deposited Aβ leads to the loss of vascular integrity has been confirmed by the recent findings that immunotherapy promotes cerebral microhemorrhage in a mouse model of CAA [98].

Further experimental evidence indicating that Aβ plays a role in maintaining structural integrity comes from studies showing that *Chlamydia pneumoniae*, an insidious intracellular bacterium, when sprayed into the noses of young wild-type BALB/c mice can cause progressive deposition of amyloid plaques, in essence creating a partial model of AD without using any transgenes [72]. While it cannot be ruled out that the neuronal inflammation induced by *Chlamydia pneumoniae* promotes amyloid deposition, it is interesting to note that the blood monocytes harboring the pathogen appear to penetrate the BBB by altering tight junctions [11,77]. If Aβ does act to maintain structural integrity, then such a breach of the BBB would result in the rapid deposition of Aβ in the brain. Such a mechanism would explain why in these mice no neurofibrillary tangles develop, and why *Chlamydia pneumoniae* does not induce AD per se, but rather amyloidosis. Not surprisingly, no major alterations in the BBB were observed in APP/PS1 double transgenic mice [102].

Since vascular compromise is less likely to occur in the large vessels leading into the brain than in smaller vessels of the cortical regions of the brain, the sealant properties of Aβ are more likely to be observed in small capillaries rather than the larger penetrating vessels [142]. Indeed, deposition of Aβ is not seen in larger cerebral vessel walls nor in extracranial vessels. Smaller vessels, such as intracortical arterioles and capillaries, that are more likely prone to rupture (and participate in the BBB) display more extensive Aβ deposition than stronger, thicker walled arterioles [110]. Histological and immunocytochemical studies have shown that Aβ accumulates five times more frequently around arteries than around veins, with selective involvement of smaller arteries [142]. The increased deposition of Aβ in arteries also is consistent with the fact that arteries are more likely to develop hemorrhages, a result of increased arterial blood pressure in arteries compared with veins. It has been suggested that Aβ may accumulate in periarterial interstitial fluid drainage pathways of the brain, and that this contributes significantly to CAA in AD [142]. Thus, the capillaries leading to the hippocampus and cortex, those regions of the brain most prone to AD neuropathology, might be expected to have the least cerebral perfusion, i.e. being of smaller diameter and/or more clogged. Over time, the compensatory increase in cerebral blood perfusion becomes insufficient to provide adequate perfusion and nutrient supply to localized

regions within the hippocampal and cortical regions of the brain.

The proteolytic processing of AβPP has been linked to sphingolipid–cholesterol microdomains (rafts). Protease plasmin is restricted to rafts of cultured hippocampal neurons and increases the processing of human AβPP preferentially at the α-cleavage site, but also efficiently degrades secreted amyloidogenic and non-amyloidogenic AβPP fragments [71]. Thus, physiologic brain plasmin appears to play a preventive role in AβPP amyloidogenesis. Interestingly, brain tissue from AD patients contains reduced levels of plasmin [71], implying that there are signals to limit the removal of deposited amyloid and hence promote amyloid deposition. This may be a result of chronic stresses upon the vasculature and the requirement for continuous amyloid deposition required to maintain vascular integrity. Indeed, we have found that the severity of AD neuropathology is positively correlated with soluble amyloid load [39]. Excessive signaling for the deposition of Aβ or capillary basement membrane thickening might however lead to the exact problem these mechanisms have evolved to prevent, decreasing cerebrovascular perfusion.

2.6. In vivo evidence for Aβ-induced hemorrhage

Abnormal deposition of Aβ, such as in amyloid angiopathy [96,70] and certain related disorders including hereditary cerebral hemorrhage amyloidosis-Dutch type (HCHWA-D) (e.g. Ref. [15]) results in cerebrovascular hemorrhage. In HCHWA-D, where individuals carry a Glu→Gln substitution at position 22 of Aβ, massive vascular deposition of Aβ results in recurrent strokes in the fourth and fifth decades of life that eventually leads to death. It is not clear if the hemorrhage is due to excessive Aβ deposition that leads to smooth muscle cell death (see below) and eventual endothelium rupture, or protease-mediated clearance of formed amyloid deposits leading way to hemorrhage as recently demonstrated in a mouse model of CAA [146,98].

Studies have suggested that excessive cerebral amyloid deposition leads to the degeneration of vascular smooth muscle cells of the large penetrating vessels as well as the cerebral capillaries that represent the BBB [138,29,62,139,103]. This degeneration of smooth muscle cells likely leads to a cycle of increased expression of AβPP and Aβ peptide generation and deposition [62,119] as a response to maintain regional integrity, resulting in massive Aβ accumulation in the media of vessel walls. Degeneration has best been demonstrated in a transgenic mouse model of CAA (APP23) that leads to cerebrovascular amyloidosis, smooth muscle cell loss, microhemorrhages, and in old age, spontaneous cerebral hematomas [24,145]. That spontaneous microhemorrhages were not observed in these mice until after 20 months of age [145] indicates other stress and/or age-related factors, other than the overexpression of AβPP, also are involved. As suggested by these authors, 'although several factors may contribute to CAA in humans, the neuronal origin of transgenic AβPP, high levels of Aβ in cerebrospinal fluid, and regional localization of CAA in APP23 mice suggest transport and drainage pathways rather than local production or blood uptake of Aβ as a primary mechanism underlying cerebrovascular amyloid formation'. Since these clearance mechanisms would normally function during adult life to resolve Aβ deposits during the healing process following head trauma, such toxic deposition may better model amyloid deposition in disease states such as AD and vascular dementias. Thus, it is likely that only the excessive deposition of amyloid fibrils in the cerebrovasculature will induce toxicity and microhemorrhages [55]. Indeed, it is likely that the first report of CAA following head trauma to a 74-year-old female, thought to lead to progressive multiple intracerebral hemorrhages as determined by CT scan (and death in this patient), was not due to amyloid angiopathy (as determined by biopsy and pathological examination) [140], but rather an insufficient amyloid response that did not prevent hemorrhage in the severely damaged vasculature.

2.7. Neuronal/vascular remodeling

That Aβ is involved in cell mobility and the extension of neurites through the ECM was first suggested more than a decade ago as part of a reactive plasticity response to the neuronal loss associated with AD [143]. Aβ/AβPP is a developmental protein as shown by its presence in cytoplasmic processes of astrocytes in the subpial layer and white matter of the developing human brain [126]. The increased deposition of Aβ in AD indicates massive remodeling within the diseased brain. Such an idea has been proposed to explain the increased deposition of Aβ associated with neuronal remodeling and the cognitive deficits associated with repetitive mild traumatic brain injury of AβPP-transgenic mice (Tg 2576) [124,130]; Aβ-mediated remodeling likely results in neurite and synapse withdrawal and hence the loss of function.

Secreted AβPP also has been shown to increase neuronal survival and growth by mediating nerve growth factor-induced neurite extension [82,1], increasing synaptic density [109], having synaptotrophic properties [89], regulating cell growth [113] and showing general trophic responses [3,148]. Both NGF and neuronal differentiation regulate AβPP expression [150,43,30]. A direct role for AβPP in wound healing has been shown in a MDCK cell wound-healing assay where overexpression of AβPP accelerates cell migration and wound closure [111]. Coexpression of AβPP and FE65 dramatically enhances the effect of AβPP on cell movement. Therefore, it is likely that AβPP is involved in the initial clearance and subsequent rebuilding of tissue after injury [3]. The prominent growth

response induced by sAβPP may reflect attempted regeneration of viable, healthy neurons following synaptic disconnection due to death of other neurons, a situation that might be expected during the course of AD and following head injury.

3. Resolution of amyloid deposition during repair of injury

Acute phase molecules signal the pro-inflammatory mechanisms of wound healing [2]. Simultaneous signaling from other molecules controls and assuages inflammation towards the end of the wound healing process. For example, transforming growth factor β1 (TGF-β1) has been implicated in the alleviation of inflammation and the tissue rebuilding process while α2-macroglobulin (α2M), together with its protease inhibitory and removal activity, when bound to LRP, acts as a clearance system for numerous inflammatory proteins [16] such as apolipoprotein E (ApoE), AβPP, Aβ [91], lactoferrin, tPA, uPA, PAI-1, lipoprotein lipase, receptor associated protein [144,67], IL-1β, TGF-β, platelet derived growth factor and fibroblast growth factor [16,36,51]. Indeed, it has been demonstrated in rats that there is a time-dependent clearance of diffuse amyloid deposits from brain regions affected by traumatic brain injury [57,58] and by ischemia (see Ref. [101]). The resolution of amyloid deposition in humans is indicated from studies showing that Aβ deposits are not more common among survivors of head injury when compared to controls [78]. The mechanisms that might resolve amyloid deposition are discussed below.

3.1. Microglia

It is known that damage to the brain, such as following amyloid deposition and cerebral infarcts (strokes), leads to an inflammatory response that includes the activation of microglial cells that clear away damaged tissue and structures formed to maintain regional integrity. The interplay between metal ions, ECM proteins and microglia, that all bind to the VHHQKL region of Aβ, has important consequences for the recruitment and activation of microglia and clearance of the amyloid deposit. The release of molecules from the VHHQKL region (i.e. as inflammation resides and pH increases) would be expected to promote (Aβ-induced) microglial and/or macrophage activation and the engulfing and removal of the vascular or parencyhmal 'scab', respectively. Indeed, in the AD brain at least, increased phagocytic activity does appear to clear diffuse amyloid deposits and the diffuse halo surrounding dense core plaques (Dickson, 2002). However, the conversion of Aβ deposits into fibrillar hard cores appears to prevent microglial mediated clearance.

3.2. Plasmin system

As mentioned earlier, tPA likely plays an important role in the degradation/clearance of Aβ. Animal studies supporting this show that tPA knockout mice develop amyloid deposits at 12–14 months and display increased brain edema compared with wild-type mice after controlled cortical impact brain injury, indicating a decreased clearance of ECM molecules promotes increased fluid buildup [141]. That Aβ aggregates can substitute for fibrin aggregates in activating tPA [64] suggests the potential for the removal of Aβ deposits from the vasculature. Such removal also will be dependent upon the ratio of plasmin inhibitors to proteases, regulation of transcription and the localization of plasmin system components. Interestingly, uPA and tPA have been localized to the vicinity of senile plaques in AD tissue [105].

3.3. Other proteases

Clearance also might be mediated by circulating (e.g. neprilysin) and cellular (e.g. insulin degrading enzyme (IDE), endothelin-converting enzyme) proteases [56,69]. At least in AD, the decreased clearance of Aβ deposits by such proteases has been postulated to promote the accumulation of amyloid deposits. Recent data indicating IDE knockout mice have elevated brain Aβ levels (Dr Suzanne Guénette, personal communication), and in vitro data indicating that decreases in the cellular activity of IDE promote increased Aβ accumulation [121], support this possibility. Neprilysin also has been shown to degrade Aβ, and in neprilysin heterozygous (+/−) knockout mice, there is a 50% increase in soluble Aβ but not insoluble Aβ levels [112]. These findings suggests that different Aβ-degrading proteases act preferentially on different pools of Aβ (soluble, deposited, fibrillar). Neprilysin protein and mRNA expression and activity decrease with age especially after menopause/andropause, particularly in the terminal zones of the mossy fiber and perforant path. This decrement is associated with particular brain regions (e.g. CA3, terminal zones of perforant path and entorhinal cortex) [57,58,42], suggesting that neprilysin deficiency plays a role in the age-associated increase in amyloid deposition. Further support for this comes from the fact that mutant Aβ is degraded more slowly by neprilysin. Moreover, neprilysin mRNA and protein levels are significantly elevated in AβPP transgenic mice for as long as 30 weeks following a single intracranial injection of Aβ1–42. The rise in neprilysin levels is associated with the prevention of plaque formation and reduced astrogliosis [93]. Clearance of Aβ also likely depends upon ApoE isoform, since amyloid plaques are more likely to be found in the brains of individuals with the ApoE4 allele than with the ApoE3 allele [78,92], indicating either that deposition is greater and/or that catabolism of Aβ is decreased in individuals with the E4 allele.

3.4. Receptor for glycation end-products

In addition to the removal of aggregated non-modified Aβ, post-translationally modified proteins that result from the damage induced by the lesion environment also must be cleared from the brain. In this respect, the upregulation of receptor for glycation end-products (RAGE) during inflammation [48] associated with the lesion [120] likely promotes the clearance of oxidized and fibrillized proteins from the damaged/inflamed area during resolution of the injury. Indeed, one of the most important functions of RAGE may be to help clear from sites of injury post-translationally modified proteins. It is likely that all of the above clearance mechanisms operate at some level to resolve Aβ deposits.

4. Amyloid removal as a therapy for amyloid diseases?

The prominence of the 'amyloid hypothesis' as the cause of AD has driven researchers to develop therapeutic strategies targeted at the removal of Aβ in order to stabilize and/or reverse cognitive deficits. This idea has been spurred on by experiments showing that amyloid deposits and cognitive deficits can be resolved following immunization of transgenic mice overexpressing mutant human AβPP [116]. This unfortunate model—the removal with no apparent side-effects of a foreign human protein that had been greatly overexpressed in a mouse—led to the idea that such a course of action would benefit AD patients. It could be argued that removal of amyloid might not be expected to be problematic given that AβPP and BACE knockout mice [47,76] have no phenotype. However, given that Aβ may only be required during injury, and as mentioned earlier, cerebrovascular sealant mechanisms may not be essential for the survival of rodent species, indicates these transgenics are a poor model of AD. In addition, rodents may be less dependent on Aβ for remodeling or neuronal development compared with other mammals.

That Aβ *does* deposit in AD strongly indicates that the integrity of the parenchyma and vasculature are under attack. It is clear, however, from our basic understanding of the protein that the deposition of Aβ appears to be a purposive response, one that acts to maintain structural integrity of the BBB and parenchymal structures, prevent coagulation, promote remodeling and reduce oxidative stress. These activities of Aβ would provide an important physiological response to limit the loss of terminally differentiated neurons after head trauma. Therefore, the removal of amyloid from the brain via vaccination or other means after its deposition would be predicted to lead to cerebral hemorrhage [9,7,8]. Indeed, the Phase IIA Aβ vaccination trials by Elan Pharmaceuticals were halted due to clinical signs of inflammation. Although much has been said and written about the suspension of the trials, the root cause of the encephalitis and meningitis suffered by these individuals has not been addressed. This cause is likely associated with the direct removal of amyloid deposits from the parenchyma and vasculature, the proposed action of the vaccine. That is the immunotherapy was successful in removing Aβ, but a disaster for the health of the individuals. Put another way, amyloid vaccinations were not able to discriminate between physiologically purposive deposits of Aβ (i.e. vascular and diffuse deposits) and pathological Aβ (senile plaques, oligomers). Removal of vascular Aβ would therefore alter the structural integrity of that region and lead to leakage of serum components into the brain (hemorrhagic stroke) resulting in an immune (or autoimmune) response characterized by inflammation. This breakdown of the blood–brain barrier is consistent with the development of encephalitis and meningitis, and perhaps the presence of viruses within the CSF as reported in some of the patients under investigation. Indeed, neuronal inflammation is not a feature of other autoimmune diseases.

Activation of the plasmin system that prevents the *early* deposition of Aβ might however be of therapeutic value in diseases of amyloid angiopathy (e.g. HCHWA-D) by preventing early cell loss, endothelial rupture and hemorrhagic stroke. Activation of plasmin would both degrade Aβ and prevent its formation since plasmin in lipid rafts cleaves AβPP at the alpha-secretase site [71]. Conversely, in individuals with marked amyloid angiopathy, the use of tPA inhibitors to prevent amyloid removal by plasmin might actually prevent cerebral hemorrhage (providing amyloid deposits are not toxic) and prolong lifespan in individuals with HCHWA-D.

5. Summary

The acute phase generation of Aβ has evolved as a sealant, anti-coagulation, secondary antioxidant defense system and remodeling molecule required during times of remodeling and excessive ROS generation and/or trauma [4,5]. A large body of literature supports these activities of Aβ. The deposition of Aβ immediately following head injury, its resolution during the healing process and its deposition in the compromised elderly and AD vasculature are consistent with such roles for Aβ. In this way, hemorrhage can be prevented while allowing for an uninterrupted blood supply. It remains to be determined if similar mechanisms have evolved in other tissues. These beneficial properties of Aβ and its precursor protein do however bring into question the validity of the therapeutic efficacy of removing Aβ from the brain.

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