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Linking vascular disorders and Alzheimer's disease: Potential involvement of BACE1

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Abstract

The etiology of Alzheimer's disease (AD) remains unknown. However, specific risk factors have been identified, and aging is the strongest AD risk factor. The majority of cardiovascular events occur in older people and a close relationship between vascular disorders and AD exists. Amyloid plaques, composed of the beta amyloid peptide (A β), are hallmark lesions in AD and evidence indicates that A β plays a central role in AD pathophysiology. The BACE1 enzyme is essential for A β generation, and BACE1 levels are elevated in AD brain. The cause(s) of this BACE1 elevation remains undetermined. Here we review the potential contribution of vascular disease to AD pathogenesis. We examine the putative vasoactive properties of A β and how the cellular changes associated with vascular disease may elevate BACE1 levels. Despite increasing evidence, the exact role(s) vascular disorders play in AD remains to be determined. However, given that vascular diseases can be addressed by lifestyle and pharmacologic interventions, the potential benefits of these therapies in delaying the clinical appearance and progression of AD may warrant investigation.

Keywords

Alzheimers disease; Beta amyloid peptide; BACE1; Cardiovascular; Cerebrovascular; Hypoperfusion

1. Introduction

The most prevalent forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD; Hebert and Brayne, 1995; Pendlebury and Solomon, 1996; Erkinjuntti et al., 1999). Whereas VaD results from ischemic or hemorrhagic cerebrovascular disease, as well as from hypoperfusive ischemic cerebral injury resulting from circulatory and cardiovascular disorders (Roman et al., 1993; Roman, 2002), the etiology of AD remains elusive. While the mutations that cause the rare, familial AD (FAD) have been identified (St. George-Hyslop et al., 1990; Goate et al., 1991; Schellenberg et al., 1992; Levy-Lahad et al., 1995), the causative factors in the remaining ~95% of so-called sporadic AD cases are unknown.

Pathologically, AD is characterized by the accumulation of the beta amyloid peptide (A β), as fibrillar A β plaques and soluble oligomers in specific brain regions. Cerebrovascular pathology including cerebral amyloid angiopathy (CAA) is also frequently observed in the

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Conflicts of interest

There are no actual or potential conflicts of interest.

AD patient (reviewed in Kalaria and Ballard, 1999). In addition, intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein, neuroinflammation, synaptic loss, neuronal dysfunction and neuronal death further characterize this disease. Studies on frontal temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17; a tauopathy), in which there is an early A β deposition suggest that tau dysfunction could be down-stream in the pathogenic sequence (discussed in Sorrentino and Bonavita, 2007). Indeed, evidence indicates that A β plays an early and central role in AD pathogenesis, and the basic tenant of the amyloid hypothesis (also referred to as the A β cascade hypothesis; Golde et al., 2006) is that aggregates of A β trigger a complex pathological cascade which leads to neurodegeneration. Over time, AD brain displays increased A β plaque numbers and A β burden. A β is derived by endoproteolysis of the amyloid precursor protein (APP). Numerous mutations in the presenilin and APP genes are associated with increased A β production and cause FAD with ~100% penetrance. A β deposition precedes clinical symptoms of AD and A β is increased in the plasma of persons older than 65 years who later develop AD compared with age-matched controls. Patients with Down's Syndrome (DS), and FAD families with a duplicated APP gene locus, exhibit total A β overproduction and develop early-onset AD (Rovelet-Lecrux et al., 2006). Fibrillar and oligomeric forms of A β appear neurotoxic both in vitro and in vivo. Importantly, in APP transgenic (Tg) mouse models of AD the genetic ablation of A β production is associated with the absence of neuronal loss and improved cognitive function (Ohno et al., 2004; Laird et al., 2005; Ohno et al., 2007). Such data provide direct evidence for the amyloid hypothesis in vivo, and also indicate that A β is directly responsible for neuronal death.

Sequential cleavage of APP in the amyloidogenic pathway by β -secretase, identified as β -site APP cleaving enzyme 1 (BACE1), and γ -secretase, a complex of presenilin 1 (PS1) or 2 (PS2), Aph1, Nicastrin and Pen2 proteins, liberates the N- and C-terminus of A β , respectively, thus releasing the mature A β peptide (reviewed in Selkoe, 2001; Vassar, 2004). BACE1 cleavage is a pre-requisite for A β formation, and is the initiating step in A β generation. Ablation of BACE1 in Tg AD models abolishes all A β production and prevents the subsequent development of amyloid-associated pathologies (Ohno et al., 2004, 2007; Laird et al., 2005; McConlogue et al., 2007). γ -Secretase cleavage of APP is imprecise, generating peptides of differing length. While the 40 amino acid form (A β 40) predominates, A β composed of 42 amino acids (A β 42) is the more fibrillogenic, neurotoxic entity. APP is also cleaved within the A β domain by α -secretase which prevents A β formation. Three putative α -secretase moieties have been identified: TACE (TNF- α converting enzyme), ADAM (a disintegrin and metalloprotease domain protein)-9 and ADAM-10 (Buxbaum et al., 1998; Lammich et al., 1999).

A β fulfills an early, critical role in AD pathogenesis. As BACE1 is critical for A β generation, with BACE1 deficient animals producing no A β at all, this enzyme represents a strong therapeutic target for AD treatment. While over-inhibition of BACE1 may cause untoward side-effects (Ohno et al., 2004, 2006; Laird et al., 2005; Willem et al., 2006; Hu et al., 2006), it has been speculated that BACE1 is a more suitable therapeutic target than either γ - or α -secretase. Pre-senilin, the catalytic member of the γ -secretase complex, is involved in the Notch signaling pathway (Levitani and Greenwald, 1995) and knocking out PS1 causes embryonic lethality (Wong et al., 1997). Although mice showing reduced PS expression and conditional neuronal knockouts are viable, they exhibit behavioral deficits (Yu et al., 2001; Dewachter et al., 2002) and they may have potential for initiating tumorigenesis (Xia et al., 2001). With regards to α -secretase, a potential treatment strategy would be to enhance the activity of this enzyme, although such an approach is perceived to be more challenging than inhibiting cleavages by the pro-amyloidogenic secretases (reviewed in Hardy, 2006).

2. Vascular disease and AD

While its etiology remains undetermined, some risk factors for sporadic AD have been identified. Aging is the major risk factor for AD, though the cause of this association remains unknown. Another strong risk factor for AD is the presence of the apolipoprotein E4 (ApoE4) allele (Corder et al., 1993), which is associated with atherosclerosis (reviewed in Mahley and Hall, 2000). Interestingly, there appears to be a close association between vascular diseases (both cardio- and cerebro-) and AD (reviewed in Kalaria and Ballard, 1999; de la Torre, 2006). While vascular disease and associated risk factors, including hypercholesterolemia, hypertension and the ApoE4 allele, correlate with elevated AD risk, the direct contribution of vascular disease to AD pathogenesis remains hotly debated. Indeed, events that cause cerebrovascular disease, including stroke or transient ischemic attacks remain exclusion criteria for AD diagnosis (Dubois et al., 2007; reviewed in Kalaria and Ballard, 1999). However, accumulating evidence makes a rigid distinction between AD and VaD no longer tenable, and it has been proposed that AD and VaD represent the extremes of a range of pathologies in which vascular and non-vascular factors co-exist to varying extents (Iadecola, 2004). Indeed, Schneider and colleagues recently reported that the most common neuropathologic finding in persons with dementia was mixed lesions, usually AD with infarcts (Schneider et al., 2007a). In addition to the fact that vascular disease and AD share common risk factors, indicative that their pathogenic mechanisms are somehow related, small ischemic lesions aggravate dementia (Snowdon et al., 1997; Riekse et al., 2004; Petrovitch et al., 2005). In fact, silent cerebral infarcts, atrial fibrillation, hypertension and angina have all been associated with a greater rate of decline in AD patients (Mielke et al., 2007; Song et al., 2007). Furthermore, AD patients exhibit more severe atherosclerosis in the cerebral arteries at the base of the brain (the circle of Willis) when compared to age-matched controls (Roher et al., 2003). Cerebral blood supply is limited by the vascular narrowing caused by these lesions (Iadecola, 2003; Beach et al., 2007). Indeed, cerebral blood flow (CBF) is reduced in the early stages of AD and the reactivity of cerebral blood vessels is impaired (reviewed in Kalaria and Ballard, 1999; Matsuda, 2001; Kalback et al., 2004). Chronic brain hypoperfusion (CBH) is a pre-clinical condition of mild cognitive impairment (MCI), a condition thought to precede AD, and is an accurate indicator for predicting AD development (Johnson et al., 1998; de la Torre, 1999; Meyer et al., 2000; Maalikjy Akkawi et al., 2005; Ruitenberg et al., 2005). Further, hypometabolism and/or hypoperfusion in temporoparietal areas, as imaged by positron emission tomography (PET; reviewed in Dubois et al., 2007), are distinctive markers of AD, and an association between impaired functionality of microvessels and unfavorable evolution of cognitive function in AD patients has been reported (Silvestrini et al., 2006).

3. Vasoactive properties of A β

A β is a key player in AD pathogenesis. While the contribution (direct vs. indirect) of vascular factors to AD pathogenesis remains to be determined, recent findings indicate that A β may exert vasoactive effects. The integrity of brain function relies on the balance between glucose and oxygen delivery through blood flow and the energy demands imposed by neural activity. The regulation of cerebral blood distribution to specific brain regions depending on their functional activity is known as functional hyperemia, and the neurovascular (NV) unit, composed of perivascular neurons, astrocytes, endothelial cells and vascular smooth muscle cells, plays a crucial role in this regulation. There is evidence to suggest that the NV unit undergoes dysfunction during the early stages of AD (reviewed in Kalaria and Ballard, 1999; Iadecola, 2004). In addition to depressing synaptic transmission and neuronal activity (Yu et al., 2001; Kamenetz et al., 2003; Plant et al., 2006), A β may also exert effects on the systemic and cerebral vasculature. Niwa and colleagues reported that A β has a direct effect on the vasculature in APP Tg mice (Niwa et al., 2000). Not only

was resting CBF reduced in APP Tg mice, but the CBF response to somatosensory activation was reduced. Importantly, this impairment of functional hyperemia appeared prior to the appearance of amyloid in plaques and the vasculature and regional CBF was reduced as a result of soluble amyloid on eliciting vasoconstriction and attenuating endothelium-mediated vasodilation. Furthermore, superfusion of the neocortex with A β led to deficits in hyperemia in wild type mice and previous studies examining the effects of A β on isolated vessels add further support for the vascular effects of this peptide (Thomas et al., 1996; Crawford et al., 1998).

In contrast to the effects of soluble A β on the vasculature, Shin and colleagues very recently reported that A β impacts cerebrovascular function only after vascular deposition, at least in APP Tg mice (Shin et al., 2007). The reason(s) for these contrasting data remains to be determined, although as speculated by the authors, may relate to the use of different techniques to measure vascular function. As indicated previously, CAA is observed in the majority of AD brains, although whether vascular deposition is also a prerequisite for cerebrovascular dysfunction in AD patients is not known. However, CAA can lead to weakness and rupture of the vessel wall leading to hemorrhagic stroke and ischemic infarcts, both of which are known AD risk factors (Schneider et al., 2007a,b). Christie and colleagues reported that, following vasculature amyloid deposition, smooth muscle cells in the walls of pial vessels were deleteriously affected and responded inappropriately to vasodilators (Christie et al., 2001). As discussed by Coma and colleagues (Coma et al., in press), whether vascular amyloid originates from neuronal or vascular sources remains a debated topic. BACE1 is essential for A β generation. While BACE1 mRNA expression is not universal, it is expressed widely in human neural and non-neural cells and tissues (Sato and Kuroda, 2000), although the brain has the highest levels of BACE1 activity. With reference to cell types of the NV unit, BACE1 mRNA is highly abundant in neurons of the CNS, and is expressed at low levels in resting glial cells (Vassar et al., 1999; Marcinkiewicz and Seidah, 2000). Inflammation may enhance the glial cell expression of BACE1 (Bourne et al., 2007). In addition, vascular smooth muscle cells express all secretases involved in APP cleavage and produce A β , at least in vitro. Thus, Coma and colleagues propose that human cerebral smooth muscle cells may contribute to CAA observed in AD patients (Coma et al., in press).

While the above data support a causative role for A β in cerebrovascular dysfunction, there is accumulating evidence to indicate that A β accumulation also occurs as a consequence of this dysfunction. It was originally proposed that in contrast to FAD, where mutations in APP and PS genes lead to increased A β synthesis, the basis of increased A β burden over time in sporadic AD was likely due to decreased A β degradation and/or clearance (reviewed in Rosenberg, 2002). Indeed, dysfunction of the NV unit resulting in compromised CBF regulation and blood brain barrier transport could impair A β clearance and lead to increased central levels of soluble and fibrillary A β species. Thus, through effects on the cerebrovasculature, A β may autopotential its own elevation in the CNS and may be both the cause and the consequence of cerebrovascular impairment (Fig. 1).

4. BACE1 upregulation in AD

Cleavage of APP by BACE1 is a prerequisite for A β formation. Tg mice deficient in BACE1 do not produce any form of A β , and lack the A β -associated pathologies, neuronal loss and memory deficits observed in age-matched Tg mice which express BACE1 (reviewed in Cole and Vassar, 2007). The homolog BACE2 shares 64% amino acid similarity with BACE1, but does not have the correct expression pattern for β -secretase (Bennett et al., 2000) and exhibits α -secretase-like activity (Yan et al., 2001; Basi et al., 2003). As reviewed elsewhere, the characteristics of BACE1 match one-to-one with the

previously established properties of β -secretase activity in cells and tissues (Cole and Vassar, 2007). Table 1 summarizes the key properties of BACE1.

The cause of $A\beta$ elevation in AD remains unknown and it is plausible that several pathways converge to cause this elevation. The identification of BACE1 substrates (for example, voltage-gated sodium channel β -subunit $Na_v1\beta$; neuregulin-1), in addition to APP, has begun to reveal potential BACE1 physiological functions (detailed below; Wang et al., 2005; Willem et al., 2006; Hu et al., 2006). Current indications are that BACE1 may function as a stress response protein that is upregulated in AD (Tamagno et al., 2002; Blasko et al., 2004; Wen et al., 2004; Tong et al., 2005; Velliquette et al., 2005; Tesco et al., 2007). Recent studies demonstrate that BACE1 levels are elevated in both AD experimental models and, importantly, in AD brain (Fukumoto et al., 2002; Holsinger et al., 2002; Tyler et al., 2002; Yang et al., 2003; Li et al., 2004; Harada et al., 2006; Zhao et al., 2007). The observed elevation in BACE1 activity is correlated with brain $A\beta$ production in the frontal cortex (Li et al., 2004), suggesting that BACE1 elevation may lead to enhanced $A\beta$ production and deposition. Despite normalization of BACE1 levels to synaptic markers in AD brain (Fukumoto et al., 2002), it is difficult to determine from post-mortem tissue whether a specific change is an epiphenomenon in late-stage AD, or whether it is an early event directly involved in pathogenesis. We recently addressed this issue by examining BACE1 levels in two Tg models of AD, the 5XFAD mouse (Oakley et al., 2006) that develops amyloid plaques at 2 months of age and exhibits obvious regional neuronal loss, and the Tg2576 mouse (Hsiao et al., 1996), which develops plaques later on and does not show significant neuronal death. BACE1 elevation was correlated with amyloid pathology in both models, in the absence (Tg2576) and presence (5XFAD) of significant neuronal loss (Zhao et al., 2007). Thus, BACE1 elevation appeared to be associated with amyloid pathology rather than cell death. The use of a novel, mono-specific BACE1 antibody facilitated detection of BACE1 in presynaptic neuronal structures around neuritic plaques. Taken together, our data are suggestive of a positive feedback loop, whereby $A\beta_{42}$ deposits cause BACE1 levels to rise in nearby neurons through an as of yet unknown mechanism. Increased $A\beta$ production may then ensue, initiating a vicious cycle of additional amyloid deposition followed by further elevations in BACE1 levels. $A\beta_{42}$ is neurotoxic and such toxicity may induce the BACE1 increase. However, it remains unclear as to which is the initiating event, $A\beta$ elevation and deposition or increased BACE1 activity.

5. Cellular changes associated with vascular diseases can elevate BACE1 levels and activity

Determining the causative factors in elevated BACE1 expression and activity will allow better understanding of AD pathogenesis. Individuals with AD and cerebrovascular pathologies exhibit greater cognitive impairment than those exhibiting either pathology alone (Snowdon et al., 1997; Riekse et al., 2004; Petrovitch et al., 2005; reviewed in Kalaria and Ballard, 1999). Importantly, both cardio-and cerebrovascular disease cause reduced CBF and CBH (reviewed in de la Torre, 2006). Evidence suggests that subcellular changes crucial to the development of neurodegeneration are provoked by CBH. CBH can cause hypoxia, in addition to ischemic episodes, which involves both hypoxia and reoxygenation, which cause cellular stress. Indeed, markers of oxidative stress, such as 4-hydroxy-2-nonenal (HNE) have been detected at the early pathological stages of AD (Sayre et al., 1997; Williams et al., 2006). In addition, several studies indicate that defective energy metabolism may play a fundamental role in AD pathogenesis. Post-mortem analysis of AD brain shows downregulated expression of several mitochondrial enzymes implicating brain energy metabolism impairment in AD (Rapoport, 1999; reviewed in Chandrasekaran et al., 1996). Any factor that affects normal brain function (such as AD risk factors including TBI, ischemia, hypercholesterolemia, atherosclerosis) could facilitate perturbations in energy

metabolism. For example, TBI is known to cause oxidative stress (Uryu et al., 2002), and mitochondrial dysfunction is induced by the major precursors of atherosclerosis (hypercholesterolemia, hyperglycemia) and is clearly associated with atherosclerosis or cardiomyopathy in humans and animal models of oxidative stress (reviewed in Madamanchi and Runge, 2007). Indeed, young adults carrying the ApoE4 allele, and MCI patients, exhibit reduced brain glucose metabolism (Reiman et al., 1996; Small et al., 2000; Mosconi et al., 2004; Mosconi, 2005), indicating that impaired energy metabolism may be an early contributing event to AD pathology rather than a consequence of the disease process. Importantly, several key down-stream cellular consequences of vascular insults and the resulting CBH, such as hypoxia, energy depletion and cellular stress have been linked with an elevation in BACE1 levels and activity (Tamagno et al., 2002, 2005; Tong et al., 2005; Velliquette et al., 2005; Sun et al., 2006; Xiong et al., 2007; Yan et al., 2007). Thus, in addition to potential elevations in A β occurring as a consequence of its own vasoactive properties, as detailed above, it appears possible that cardio- and cerebrovascular insults could elevate A β levels via a mechanism involving BACE1 elevation. Indeed, it can be hypothesized that, in some cases, cardio- and cerebrovascular factors could initiate AD pathogenesis through BACE1 elevation (Fig. 1).

Hypoxia can facilitate AD pathogenesis (Sun et al., 2006; Zhang et al., 2007) and BACE1 mRNA expression is increased in Tg mice maintained in hypoxic conditions. Furthermore, hypoxia potentiated the memory deficit observed in these mice (Sun et al., 2006). BACE1 gene expression is tightly regulated at both the transcriptional and translational levels (reviewed in Rossner et al., 2006). The BACE1 promoter contains a number of putative binding sites for transcription factors that become activated in response to cellular stress. The hypoxia-inducible factor 1 (HIF-1) is involved in the regulation of oxygen homeostasis (Huang et al., 1999). Under conditions of low oxygen consumption, HIF-1 binds to a hypoxia-response element (HRE) in the promoter region and activates multiple genes involved in energy metabolism and cell death (Sharp and Bernaudin, 2004). The finding that the BACE1 promoter contains a functional HRE provides a molecular basis for the observed elevation of BACE1 expression during hypoxia (Sun et al., 2006; Zhang et al., 2007).

Transient hypoxic insult to cortical neurons can cause mitochondrial dysfunction. Given the apparent importance of metabolic dysfunction and amyloidosis in AD, it is noteworthy that BACE1 upregulation has been observed under various experimental conditions likely involving energy disruption and/or mitochondrial stress (Tong et al., 2005; Velliquette et al., 2005; Sun et al., 2006; Tesco et al., 2007; Xiong et al., 2007). Indeed, elevated BACE1 levels and activity have been reported in vitro (Tamagno et al., 2002, 2005; Tong et al., 2005) and in vivo (Velliquette et al., 2005; Xiong et al., 2007) under conditions of altered energy metabolism and oxidative stress.

The relationship between A β and oxidative stress is complex. As is the case between A β and changes in the vasculature, A β accumulation may be both the cause and the consequence of oxidative stress. While A β accumulation can lead to oxidative stress (Tamagno et al., 2006), oxidative stress in vitro resulted in significant increases in BACE1 promoter activity (Tong et al., 2005) and following HNE exposure, an increase in BACE1 mRNA and protein levels, together with elevated A β production was observed (Tamagno et al., 2002, 2005). Furthermore, the observation that oxidative stress upregulated BACE1 levels and the amyloidogenic processing of APP in smooth muscle cells led to the suggestion that this cell type may contribute to CAA observed in AD (Coma et al., in press).

The differentiation of energy inhibition from oxidative stress with regards to the pharmacological blockage of mitochondrial energetic processes in vivo is practically impossible given that inhibitors of mitochondrial respiration are generally considered to

cause oxidative stress (Sherer et al., 2003; Huang et al., 2006). Following acute energy inhibition (and/or oxidative stress) in vivo, we observed a significant elevation in BACE1 protein. This long-lasting effect appeared to correspond with a significant increase in cerebral A β 40 load. Our data indicate that translational control may be implicated in the elevation of BACE1 under conditions of energy depletion (Velliquette et al., 2005). Indeed, several studies have indicated that BACE1 may be regulated in this fashion (De Pietri Tonelli et al., 2004; Lammich et al., 2004; Rogers et al., 2004) and features of BACE1 5' untranslated region (5' UTR) such as the GC content, the length, evolutionary conservation, and the presence of upstream AUGs, indicate that the BACE1 5' UTR may play an important role in the translational regulation of BACE1.

The observation that BACE1 levels are also elevated following traumatic brain injury (TBI; Blasko et al., 2004; Wen et al., 2004) and ischemic episodes (Wen et al., 2004; Tesco et al., 2007) adds further support for the role of BACE1 as a stress response protein. Ischemia induces apoptosis and although the contribution of programmed cell death to AD remains unclear, it is interesting that elevated BACE1 immunoreactivity was associated with a marker of apoptosis following occlusion of the middle cerebral artery (Tesco et al., 2007). Importantly, Tesco and colleagues reported that this potentiation of BACE1 was due to the post-translational stabilization of BACE1 and a significant impairment in BACE1 degradation (Tesco et al., 2007).

In addition to APP, a number of other putative BACE1 substrates have been identified, including neuregulin (NRG1; Lindholm et al., 2002; Wong et al., 2005), voltage-gated sodium channel (VGSC; Na_v) subunits (Wong et al., 2005; Kim et al., 2007), lipoprotein-like receptor related protein (LRP; von Arnim et al., 2005), amyloid precursor-like proteins (APLP; Li and Sudhof, 2004; Pastorino et al., 2004), P-selectin glycoprotein ligand 1 (PSGL-1; Lichtenthaler et al., 2003) and beta-galactoside alpha 2,6-sialyltransferase (ST6Gal I; Kitazume et al., 2005). Importantly, many of these substrates may play a role in neuronal function (NRG1, VGSC β subunits) and the cellular response to stress and/or injury, such as recovery from excitotoxicity (A β ; Kamenetz et al., 2003), A β clearance (LRP; Hyman et al., 2000), synapse formation (APP, APLP1, APLP2; Herms et al., 2004; Wang et al., 2005) and immune functions (PSGL-1, ST6Gal I; Lichtenthaler et al., 2003; Kitazume et al., 2005). We speculate that following acute stress/injury BACE1 levels are elevated in order to facilitate recovery, a process that requires the cleavage of specific BACE1 substrates. However, it may be the case that chronic stress/injury may cause long-term BACE1 elevation and deleterious amyloid formation.

6. Concluding remarks

Clearly, further work is required to delineate the precise relationship between vascular disease and AD risk. However, the notion that there may be a vascular component to AD is not a new one. As detailed by Beach and colleagues (Beach et al., 2007) many early investigators believed that senile dementia and AD were caused by cerebral atherosclerosis. Following dismissal of this idea after post-mortem anatomical studies were conducted in the mid-20th century, interest in the so-called vascular hypothesis was re-ignited due to the known relationship between ApoE4 and coronary atherosclerosis and the identification of the ApoE4 allele as a strong risk factor for AD. Importantly, the study by Beach and colleagues (Beach et al., 2007) provides confirmation of a statistical association between intracranial atherosclerotic vascular disease and AD (Beach et al., 2007). While the data indicate that this association is not spurious, it remains to be determined as to whether this represents a causal or coincidental relationship.

The observations that BACE1 initiates A β production and that its levels are elevated in AD provide direct and compelling reasons to develop therapies directed at BACE1 inhibition to reduce A β and its associated toxicities. Data suggest that BACE1 levels may start building early and become sustained in the course of AD development and it is plausible that different factors cause this elevation at different stages of the disease. Our data indicate that the BACE1 elevation in AD may be actively involved in AD pathology and may occur prior to the appearance of overt neuron death (Zhao et al., 2007). However, increases in BACE1 activity have also been demonstrated in vivo occurring in response to the induction of apoptosis, an event that may be associated with the later stages of neurodegeneration (Tesco et al., 2007). We speculate that BACE1 functions as a stress response protein that is elevated under many conditions including those cellular changes evoked under conditions of cardio- and cerebrovascular disease. Indeed, there is increasing evidence to link vascular disease with AD pathogenesis and it is possible that vascular diseases may trigger AD. This may be an overly simplistic viewpoint. Admittedly, it is highly likely that sporadic AD results from multiple environmental and genetic factors that affect both A β production and clearance in the brain, the interaction of A β with other proteins implicated in AD and the susceptibility of neuronal populations to A β toxicity. However, given that the complications of vascular diseases can be addressed by lifestyle modifications and pharmacologic interventions, whether or not the benefits of these therapies extend to delaying the clinical appearance and progression of AD should be carefully examined.

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Fig. 1.

AD pathology and the vasculature: The effects on, and of, A β and BACE1. Figure illustrates how specific AD risk factors might cause elevations in BACE1 and A β , thereby hypothetically linking these risk factors with AD pathogenesis at the molecular level. (1) Deposition of A β in the vasculature (CAA) is observed in AD brain. CAA can cause ischemic infarcts and stroke (both AD risk factors) and A β (soluble and deposited) can exert significant vasoactive effects that are associated with decreased cerebral blood flow. Decreases in blood flow may reduce the clearance of cerebral A β . Therefore, a vicious cycle may develop whereby accumulated A β may cause cerebrovascular dysfunction, which then triggers the accumulation of more A β . (2) A β levels may also be impacted via a mechanism involving BACE1 elevation. Although the trigger(s) for BACE1 elevation in AD remains to be determined, data indicate that A β may play a role in the observed increases in BACE1 in AD brain (Zhao et al., 2007). As BACE1 initiates, and is essential for, A β formation it is possible that another vicious cycle exists whereby accumulated A β triggers increased BACE1 levels and/or activity, a process which then leads to further increases in A β level. Thus, A β may potentiate its own production via increases in BACE1. (3) Furthermore, insults to the vasculature, whether caused by A β or disease (cardiovascular; cerebrovascular) lead to lowered CBF and chronic brain hypoperfusion. CBH is associated with hypoxic and ischemic events. Such events cause significant cellular stress and energy deprivation. A β is also known to induce cellular stress. Data indicate that all such events (hypoxia, ischemic, cellular and oxidative stress and energy deprivation) can elevate BACE1 levels and/or activity. Given the complexity of AD pathogenesis it is highly likely that multiple triggers converge to alter BACE1 levels/activity during AD progression. See text for references.

Table 1

The key features of BACE1: A prime therapeutic target for AD treatment (reviewed in Cole and Vassar, 2007).

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- BACE1 gene is located on chromosome 11q23.2
 - BACE1 promoter contains multiple transcription factor binding sites including those for SP1, CREB, NFK β , HIF1 and PPAR γ
 - BACE1 mRNA undergoes alternative splicing to generate four splice variants with different enzymatic activity
 - BACE1 with maximal activity is a 501 amino acid membrane bound aspartyl protease with a luminal active site
 - BACE1 undergoes significant post-translational processing including glycosylation, sulfation and palmitoylation
 - BACE1 is most active at acidic pH and is localized in the TGN and endosomes
 - BACE1 expression is regulated at multiple levels, both transcriptional and post-translational (including post-transcriptional processing, translational and protein stability and clearance)
 - BACE1 substrates include APP, APLPs, Na $_v$, NRG1, ST6Gal1, PSGL-1 and IL-1R2
 - BACE1 is essential for A β formation, a peptide derived from APP that fulfills a central and early role in AD pathogenesis
 - BACE1 is a prime therapeutic target for AD
 - Inhibition of BACE1 prevents A β formation. AD Tg mice which are deficient in BACE1 lack all forms of A β , do not exhibit A β -associated pathologies, and are free from the neuronal loss and memory deficits observed in age-matched BACE1 expressing Tg models of AD
 - BACE1 levels and/or activity are elevated in AD brain, and recent data suggest that BACE1 elevation may be involved in the pathogenesis of this disease
 - A proposed physiological function for BACE1 is as a stress response protein
 - The cause of BACE1 elevation in AD remains to be determined although events associated with cardiovascular and cerebrovascular disease (key risk factors for AD), such as cerebral hypometabolism, hypoxia, ischemia, cellular stress and deficiencies in energy metabolism can all facilitate BACE1 increases
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