The vasculature in Alzheimer's disease: a new therapeutic target for an old disease?

"*While deaths from other major diseases, including heart disease and stroke, have significantly decreased in recent years, deaths from AD increased by 66% between 2000 and 2008...*"

KEYWORDS: Alzheimer's disease ■ amyloid ■ antioxidants ■ cerebrovasculature ■ cognitive decline ■ inflammation ■ neurodegeneration ■ neuropathology ■ neurotoxicity ■ oxidative stress

Paula Grammas

Garrison Institute on Aging, Texas Tech University Health Sciences Center, 3601 4th Street Stop 9424, Lubbock, TX 79430, USA
Tel.: +1 806 743 3612
Fax: +1 806 743 3636
paula.grammas@ttuhsc.edu

Alzheimer's disease (AD) is an age-related disorder characterized by progressive cognitive decline and dementia. AD is an irreversible neurodegenerative disease that affects more than 5.3 million people in the USA and is projected to sharply increase to 8 million by 2030 [101]. Every 69 s, someone in America develops AD, and it is the sixth leading cause of death. In 2011, the cost of caring for those with AD to American society will total an estimated US$183 billion. Unless something is done, the costs of AD in 2050 will total $1.1 trillion [101]. While deaths from other major diseases, including heart disease and stroke, have significantly decreased in recent years, deaths from AD increased by 66% between 2000 and 2008 [101]. More than a decade has passed since the first US FDA-approved drugs for the 'treatment' of AD were unveiled. Yet, despite intense research efforts, there are currently no disease-modifying drugs that can affect the relentless progression of this devastating disease. New thinking on disease pathogenesis and novel therapeutic approaches are urgently needed.

Currently, there are two classes of drugs that are FDA approved and prescribed for the treatment of AD: acetylcholinesterase inhibitors and *N*-methyl-D-aspartic acid (NMDA) receptor antagonists. Cholinesterase inhibitors inhibit the activity of the primary enzyme (acetylcholinesterase) that degrades acetylcholine, thus preserving levels of this neurotransmitter, which can slow the decline in cognitive function and improve overall well-being in AD patients. Four cholinesterase inhibitors are currently approved by the FDA for the treatment of AD: tacrine, donepezil, rivastigmine and galantamine. Memantine, the fifth FDA-approved drug, is an NMDA receptor antagonist. Excitotoxic stimulation of NMDA receptors by glutamate is thought to contribute to neuronal injury in AD. Double-blinded, randomized, placebo-controlled trials have shown the significant benefit in cognitive function, language and activities of daily living when combinations of memantine and donepezil have been used [1]. However, these drug regimens, while improving clinical symptoms and quality of life for limited time periods, do not affect progression of the disease or prevent underlying neuronal injury and death.

Central to designing effective therapies is an understanding of the underlying pathologic processes that drive disease progression. Unfortunately, the causal factor(s) that trigger and/or drive this disease remain to be defined. The amyloid cascade hypothesis, which postulates that amyloid-β (Aβ) is the primary neurotoxic species involved in disease pathogenesis, has dominated research in the AD field for the past 20 years [2,3]. Indeed, therapeutic approaches aimed at disrupting the amyloid cascade, including γ-secretase inhibitors for reducing Aβ formation, agents for preventing aggregation of amyloid oligomers, and immunotherapy for enhancing clearance of amyloid, have been exhaustively pursued [1,4,5]. However, Aβ-centered therapeutic trials have not produced the beneficial clinical results anticipated [3,4]. Aβ-lowering agents such as R-fluribiporfin have shown promise in Phase II trials but failed in Phase III [6]. Several other anti-Aβ agents have also failed in Phase III trials. The failure of these trials, as well as other data that are not consistent with the amyloid hypothesis, has led to criticism that AD research is too 'amyloidocentric' [7,8]. In support of this increasing evidence it has been suggested that Aβ is but one component in the complex pathogenesis of AD [9].

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Therapies that target the other pathognomonic lesion of AD, hyperphosphorylated tau, have lagged behind Aβ-targeted therapies. The intracellular location of tau aggregates complicates strategies aimed at accelerating clearance. Several strategies aimed at reducing tau phosphorylation and/or aggregation are under examination [10]. Another area that has received considerable attention as a therapeutic target is oxidative stress. Indices of oxidative damage to proteins, lipids and DNA have been demonstrated in AD brains [11]. Epidemiological studies have shown support for reduced risk with higher antioxidant intake, including vitamin E; however, little efficacy has been documented in AD clinical trials [4]. A variety of other antioxidants, including curcumin and resveratrol, have shown promising results in animals and are currently in trials [12]. Finally, there is strong evidence that inflammatory proteins can affect cognition and cause neurodegenerative damage [13]. Retrospective epidemiological studies suggest that a wide variety of nonsteroidal anti-inflammatory drugs may significantly reduce one's lifetime risk of developing AD [14]. However, nonsteroidal anti-inflammatory drugs have failed to demonstrate therapeutic benefit in prospective AD clinical trials.

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Vascular mechanisms are increasingly implicated in the development and/or progression of AD. Age, atherosclerosis, stroke, hypertension, transient ischemic attacks, cardiac disease, the ε4 allele of ApoE, elevated homocysteine levels, hyperlipidemia, the metabolic syndrome, obesity and diabetes are risk factors for both vascular dementia and AD. Studies evaluating the effect of multiple vascular risk factors on the risk of dementia have shown that the effects of each vascular risk factor are additive [15]. Although the idea that vascular defects are present in AD and may be important in disease pathogenesis was suggested over 25 years ago, little work has focused on an active role for cerebrovascular mechanisms in the pathogenesis of AD.

Data from brain imaging studies in human and animal models suggest that cerebrovascular dysfunction precedes cognitive decline and the onset of neurodegenerative changes in AD and AD animal models [16,17]. Numerous structural and functional cerebromicrovascular abnormalities in AD have been identified [18]. The idea that vascular dysfunction is a primary/central event in the pathogenesis of AD has been proposed by several laboratories [16–18]. Possible vascular-based pathogenic mechanisms include dysfunction of the neurovascular unit, cerebral hypoperfusion and/or release of noxious species from the cerebrovasculature. Homeostatic signaling within the neurovascular unit (glia, neurons and vascular cells) is critical to couple blood flow to neuronal activity. Evidence suggests that disturbance of the functional relationships among cells of the neurovascular unit is an early event in AD. In this regard, functional MRI studies suggest that alterations in blood flow regulation in response to cognitive tasks may be a predictor of AD risk [19]. Zlokovic and colleagues have proposed a two-hit model of AD pathogenesis involving the neurovascular unit [17]. This hypothesis postulates that neurovascular damage is a primary occurrence and that subsequent injuries including Aβ deposition amplify and/or exacerbate vascular damage, which then leads to neurodegenerative processes/events and ultimately cognitive decline.

Evidence that sporadic (nongenetic) AD is primarily a vascular rather than a neurodegenerative disorder has been put forth by de la Torre and colleagues. This view is based on epidemiologic studies that show risk factors for AD have a vascular component that reduces cerebral perfusion and work showing the presence of regional brain microvascular abnormalities before cognitive and neurodegenerative changes [16,19].

Brain endothelial cells regulate the neuronal milieu both by their synthetic functions as well as by their blood–brain barrier function. Therefore, disturbance in cerebrovascular metabolic or transport functions could result in a noxious neuronal environment in the AD brain. Studies from our laboratory over a number of years have identified an activated/dysfunctional cerebral microcirculation characterized by upregulation of numerous inflammatory and neurotoxic proteins, including thrombin, VEGF, angiopoietin-2, TNF-α, TGF-β, IL-1β, IL-6, IL-8, monocyte chemoattractant protein-1, hypoxia inducible factor-1α, matrix metalloproteinases and integrins [18,20]. We conclude that the endothelial interface, a highly synthetic bioreactor that produces a large number of soluble factors, is functionally altered in AD and contributes to a noxious CNS milieu by

releasing inflammatory and neurotoxic species. These data support a new paradigm of disease pathogenesis, based on endothelial dysfunction and release of pluripotent mediators with effects on inflammation, vascular activation and neurotoxicity. We suggest that the activated/dysfunctional vasculature is a novel, unexplored target for therapeutic intervention in AD.

Future perspective

The lack of disease-modifying therapies may, in part, be attributed to the narrow research focus employed to understand this complex disease. Perhaps with new diagnostic criteria and guidelines for AD published recently by the National Institute on Aging and the Alzheimer's Association, which have been updated for the first time in more than 25 years, it is a propitious time to re-examine our ideas about AD therapeutics [21]. Instead of focusing laser-like on narrow etiologic factors, the complex nature of this disease should elicit new multimodal approaches that emphasize multiple pharmacologic avenues and harness the increasing wealth of data that show lifestyle choices (diet and exercise) significantly impact disease risk. Future studies aimed at demonstrating a causal link between the activated/dysfunctional vasculature and AD progression could provide valuable new insights into the pathogenesis of AD. Identification of 'vascular activation' as a target in AD would stimulate translational investigations in this newly defined area and may lead to novel therapeutic approaches for the treatment of this devastating disease.

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Website

101 Alzheimer's Association website www.alz.org