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Review Article

Is Beta-Amyloid Accumulation a Cause or Consequence of Alzheimer's Disease?

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by the pathological hallmarks of extracellular beta-amyloid (Aβ) plaques and intraneuronal tau-containing neurofibrillary tangles in the brain. Intraneuronal accumulation of Aβ also plays a role to accelerate AD progression by promoting neurodegeneration. Additionally, AD is associated with the development of amyloid angiopathy (CAA), in which Aβ builds up on the walls of the cerebral arteries, which augments the development of cerebral vascular disease (CVD). Conversely, CVD promotes Aβ deposition and the development of AD by affecting the balance of Aβ production and clearance. However, it remains to be determined whether the accumulation of Aβ is a cause or consequence of AD. The interaction between AD and CVD is a topic of considerable current interest. Here, we discuss the role of CVD in Aβ accumulation and the development of AD to provide a new point of view that combination therapies that address the accompanying cerebral microvascular disease may potentiate the efficacy of emerging treatment for AD.

Keywords: Alzheimer's disease, Cerebral vascular disease, Beta-Amyloid, Blood-brain barrier

Alzheimer's disease (AD) is the most common form of dementia. There is no cure and current therapies are not effective in delaying progression. An estimated 5.4 million Americans of all ages have AD. One in eight patients older than 65 years and 50% of the population ≥ 85 years of age are affected by this neurodegenerative disease [1-3]. The Medicare cost for the treatment of dementia and AD is $159 billion annually and is projected to rise to $511 billion by 2040 [1].

Pathological Characteristics of Alzheimer's Disease

AD is characterized by the accumulation of intracellular tau-containing neurofibrillary tangles and extracellular β-amyloid (Aβ) deposits in the brain. Aβ is formed by sequential cleavage of the amyloid precursor protein (APP) in the cell membrane. β-secretase (BACE) first removes the ectodomain of APP, and then γ-secretase cleaves the remaining C-terminal fragment of APP's transmembrane domain to liberate Aβ from the cellular membrane to the extracellular space. The Aβ protein aggregates into plaques that enhance the formation of neuro-fibrillary tangles [3-6]. These tangles promote the loss of neurons and synaptic density by enhancing inflammation, oxidative stress and the development of cerebral microvascular disease [7,8]. Aβ plaques also promote the loss of microglial cells and the senescence of neural stem/progenitor cells by affecting forebrain and hippocampal neurogenesis and eliciting a senescence response in associated astrocytes [9-11]. Recent studies have indicated that Aβ protein also increases the expression of p16 and accelerates the formation of post-mitotic neurons in the central nervous system of elderly mice, which is associated with increases in the severity of cognitive impairments and dementia [12].

Although AD is primarily associated with extracellular Aβ plaques and neurofibrillary tangles in the brain, recent studies have indicated that intra-neuronal accumulation of Aβ also accelerates AD progression by promoting degeneration and loss of neurons [13]. The levels of intracellular soluble Aβ protein have been found to correlate with the loss of neuronal synapses and cognitive impairment, whereas Aβ plaques showed little correlation [14]. A recent study showed that the protein PirB is a receptor for soluble Aβ. When the receptor is bound to soluble Aβ, it leads to synapse degradation by biochemically altering and increasing the activity of cofilin, an enzyme

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that degrades actin which is crucial to the integrity of neuronal synapses [15]. Another study using double transgenic mice with mutations in the APP and presenilins (PS1, PS2) genes, reported that the production of Aβ and the expression of p25 was elevated [13]. The rise in Aβ production causes an increase in intracellular calcium that activates calpain which in turn activates p25. P25 is thought to cause deregulation of cdk5, [16] a protein kinase involved in the development of the CNS. When cdk5 regulation is interrupted, the cytoskeleton is disturbed and this leads to neuron death by an unknown mechanism [16]. Moreover, ischemic or hypoxic conditions in the brain have also been found to up regulate the expression of enzymes that produce Aβ protein [14]. Ischemia of the brain causes an increase in the release of pro-inflammatory mediators, which in turn modify the metabolism pathway and increase the production of APP [17]. The increase in APP triggers an increase in β- and γ-secretases, which amplify the production of Aβ and leads to intraneuronal Aβ accumulation [17]. Therefore, vascular dysfunction and hypoxic conditions in the brain can have neurotoxic effects on synapses leading to neuronal destruction causing the cognitive impairments seen in AD [14].

It is well recognized that Aβ plaques are hallmark diagnostic biomarkers of AD [18]. However, current treatments and clinical trials targeting Aβ with several γ-secretase inhibitors, which have effectively reduced Aβ protein levels, have failed in clinical trials. Moreover, γ-secretase inhibitors appear to have adverse effects on cognition themselves, secondary to activation of Notch or other critical substrates [19-21]. The low efficacy of current therapeutics for the treatment of AD has led the community to reconsider the idea whether an increase in the production of Aβ is the primary underlying cause of AD. Hence, there is considerable interest to better understand the mechanisms leading to the accumulation of Aβ protein in the brain, and to better define under what conditions they become clinically significant.

Cerebral Vascular Disease and Alzheimer's Disease

There is increasing evidence that cerebral microvascular dysfunction plays an important role in the development of AD. Indeed, the interaction between cerebral vascular disease (CVD) and AD is a topic of considerable current interest [22-26]. However, it remains to be determined whether CVD in AD patients is secondary to the accumulation of Aβ, or if it serves as an initiating factor in the development of this neurodegenerative disease. Hypertension, diabetes, and hyperlipidemia, along with aging, are the primary risk factors for AD. They all are the leading risk factors for cerebral vascular disease, endothelial dysfunction and stroke. Almost all elderly patients with severe CVD exhibit substantial Aβ accumulation [20,27,28]. Conversely, infarcts and small vessel disease, which are the hallmarks of vascular dementia (VaD) [28,29], are found in >50% of brains collected from AD patients [23,24]. Based on this evidence, several investigators have suggested that AD may be a primary vascular disorder rather than secondary to Aβ deposition induced neurodegeneration [23-25].

An imbalance of Aβ production and clearance results in accumulation of Aβ surrounding cerebral vessels [30] and produces amyloid angiopathy (CAA) in up to 90% of the brains of AD patients, versus only about 30% in controls [23,28]. Most patients with AD exhibit small vascular disease (SVD) and ischemic parenchymal abnormalities [28]. SVD and cerebral infarcts, which are the hallmarks of vascular dementia, [28,29] are found in >50% of brains collected from AD patients [23,24]. The incidence of AD among elderly patients is 2-fold higher after ischemic stroke, which causes localized hypoxia in the brains [31]. APP levels are elevated, and β-secretase is activated following cerebral ischemia in animal models [32].

Micro-RNAs (miRNAs) also play an important role in hypoxia stress responses. MiR-124 was found to be inhibited from the early to the late stages of cerebral hypoxia. This was accompanied with upregulation of expression of BACE1 protein, and an increase in Aβ protein levels in the hippocampus in rat models of cerebral ischemia [33]. ApoE4 may also accelerate the production and accumulation of Aβ protein by impairing the transport of Aβ protein from the brain to the cerebral spinal fluid (CSF) across the blood-brain barrier (BBB) [31]. Under hypoxic conditions, autophagy-lysosome mediated proteolysis of ApoE is disturbed and the subsequent increase in ApoE4 protein enhances the accumulation of Aβ protein [34]. Hypoxia also activates inflammatory pathways and increases the formation of neurofibrillary tau tangles and Aβ plaques, as well as reduces Aβ degradation and the clearance of Aβ protein across the BBB [31,35].

Blood-brain Barrier and Alzheimer's Disease

The BBB is a highly specialized endothelial cell membrane that lines cerebral microvessels. It represents the interface between neural and circulating cells of the immune system. SVD of AD patients are associated with endothelial dysfunction. The expression of CD31 and CD34 is decreased in AD which leads to an impairment of transport of proteins across the BBB from the CSF back into the circulation [36,37]. Lipoprotein receptor-related protein 1 (LRP1) and the receptor for advanced glycation end products (RAGE) are expressed in the cerebral microvascular endothelial cells, and regulate the clearance of Aβ from the central nervous system (CNS). LRP1 mediates the efflux of Aβ from neurons and astrocytes to the extracellular fluid in the brain, whereas RAGE promotes the accumulation of Aβ protein from the blood into the brain [38,39]. Clinical studies have demonstrated that AD pathology correlates with lower LRP1 and higher RAGE levels, which promote the accumulation of Aβ in the brain parenchyma [35,39,40]. These results support the idea that the loss of the expression and function of these transporters mediating both efflux of proteins and endothelial dysfunction, allows BBB leakage and the movement of proteins from the circulation into the CNS, and contributes to Aβ accumulation in AD.

Hypertension and aging are among the primary risk factors for AD. They act synergistically to accelerate the progression of AD pathology. Loss of BBB integrity occurs in the brain in both experimental and genetic models of hypertension [41-43]. Elevated blood pressure in AD may increase BBB leakage and the diffusion of circulating proteins, cytokines and immune cells into the CNS that promote inflammation and activate microglia in AD [44]. Microglia normally plays a protective role early in the pathogenesis of AD by increasing the clearance of Aβ protein by secreting neprilysin (NEP) and insulin-degrading enzyme (IDE). An increase in anti-inflammatory cytokine IL-4 increases the

expression of the scavenger receptor CD36 and the Aβ degrading enzymes NEP and IDE in rat primary type 2 microglia [45]. However, in late stages of AD, over-activation of the microglia leads to inflammation and the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IFN-γ, that promotes the accumulation of Aβ, decreases Aβ clearance by cerebral vascular endothelial cells, increases the permeability of BBB and promotes neuroinflammation [37,44,46].

Cerebral Autoregulation and Alzheimer's Disease

Auto regulation of cerebral blood flow (CBF) is a vital homeostatic mechanism that maintains adequate blood flow to the brain despite fluctuations in pressure [47]. It protects the brain from increases in capillary pressure, which is associated with BBB leakage, cerebral edema and neurological damage [42,47-51]. Recent studies have revealed that auto regulation of CBF is impaired in elderly hypertensive, diabetic and AD animal models. Impaired cerebral autoregulation increases transmission of pressure to small vessels which contributes to BBB disruption, inflammation, glial activation, capillary loss, microhemorrhage, localized ischemia and neurodegeneration, which accelerate the cognitive defecits in both VaD and AD patients [52-55].

Conclusion

To date, no safe and effective treatments for AD have been emerged. The hypotheses of the underlying cause of neurodegenerative AD have been focusing on cholinergic deficiency, extracellular Aβ accumulation that forms plaques in the brain, and Tau protein abnormalities leading to neurofibrillary tangles. However, current treatments and clinical trials targeting these pathways, such as using acetylcholinesterase inhibitors and γ secretase inhibitors, have not been effective which has led the community to reconsider the alternatives [21,22,56-61]. In addition, γ-secretase inhibitors that are effective in reducing Aβ protein in animal models of AD have been linked to a higher incidence of skin cancers and increases in cognitive impairment in AD patients [14]. Anti-Aβ immunotherapy has emerged as one of the most promising therapeutic strategies for the treatment of AD via microglial recruitment, Fcγ receptor-mediated phagocytosis, and a peripheral sink mechanism. However, investigators recently reported that there was no cognitive benefit of immunotherapy in a co-morbidity mouse model which exhibits amyloid deposition comorbid with VaD (APP/PS1 HHcy) [62]. This model develops additive cognitive deficits and redistribution of amyloid favoring the deposition of cerebral amyloid CAA [62]. Moreover, even though anti-Aβ immunotherapy has been demonstrated to delay loss of cognition in preclinical animal model studies, the outcome of recent clinical trials have been disappointing and failed to meet primary efficacy end points.

Taken together, it appears that CVD and BBB dysfunction play an integral role in the development of AD by increasing the accumulation of Aβ protein. Hence, the development of new therapeutic strategies for the treatment of AD should take the associated CVD into consideration. It is our view that combination therapies that address the accompanying microvascular disease and that use drugs to provide strict control of associated hypertension and diabetes, along with disease modifying drugs used to control inflammation in rheumatoid arthritis, may potentiate the efficacy of the γ-secretase inhibitors and anti-Aβ immunotherapy for the treatment of AD.

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