REVIEW ARTICLE
Vascular Neurology 2018;6:3-7
ISSN 2092-6855

Vascular Hypothesis in AD

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Received June 4, 2018
Revised July 20, 2018
Accepted August 22, 2018

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The cause of Alzheimer's disease (AD) is still not clearly known. Encountering setback of traditional amyloid cascade hypothesis, the vascular hypothesis of AD emerged as an alternative to this hypothesis as pathophysiological cause of AD. This hypothesis considers cerebral vascular dysfunction as a primary trigger for pathogenic pathways of neuronal dysfunction. Dysfunction of the blood-brain barrier, decreased cerebral blood flow, and the various inflammatory context would promote aggregation of Aβ peptide in the brain, thus be responsible for subsequent neuronal damage. The idea that vascular dysfunctions are key promotor of neurodegeneration has provided new perspectives for therapeutic approaches that will add to the treatments for AD.

Vascular Neurology 2018;6:3-7

Key Words Alzheimer's disease, Amyloid cascade hypothesis, Vascular hypothesis, Aβ.

Introduction

Alzheimer's disease (AD) is a relentlessly progressive neurodegenerative disorder characterized by cognitive dysfunction and related diverse symptoms. The patients with AD usually experience cognitive dysfunction and track the characteristic clinical course, starting with memory deficits, which soon begin to affect daily life activities. In moderate stages, patients with AD are more forgetful and need more help with daily activities, self-care, constant supervision and undergo dramatic personality changes. Diverse language dysfunction such as comprehension and verbal fluency, apraxia and various neuropsychiatric symptoms such as wandering, delusion, depressions also appears. In terminal stage, patients with AD are stiff, mute, and unable to carry out physiological functions without assistance. This progressive course has led to medical, social, and economic burdens. As for Korea, the prevalence of AD is estimated at 9.18% in people older than 65; the disease is more frequent in women than in men. AD was the most common type of dementia in the Korean population.

Despite extensive research, the pathogenesis of AD remains unclear except for genetic cases (1% to 5% of AD). Although several hypotheses suggest the pathogenesis of the disease, most have failed the test of time. Nowadays, the amyloid cascade hypothesis, which proposes that deposition of insoluble amyloid β protein (Aβ) are primary causes of AD,[1] is the mainstream of AD pathogenesis. Aβ is thought to induce the reactive oxygen species (ROS). This result in oxidative stress, neuronal damage and cognitive decline. For a long time, the amyloid hypothesis has had great influence and research subjects in AD. So most researcher regard it as the real causative pathogenetic mechanism. However, the idea that AD is caused by the amyloid dysregulation has been criticized not only for the lack of coherent evidence but also for its failure to provide an effective treatment for AD.

Encountering such difficulty situation of amyloid cascade hypothesis. I try to review alternative vascular hypothesis which claims vascular dysfunctions are primary mechanism for development of AD and cover the potential treatment options.

Amyloid Cascade Hypothesis

The amyloid-βpeptide (Aβ) was identified as main pathological component of AD in 1984, thereafter the amyloid cascade hypothesis(also known as the amyloid hypothesis, the Aβ hypothesis, etc.) has been the main theory of the AD pathogenesis for over 30.[2] Soon after this discovery, the amyloid precursor protein (APP) gene is firstly identified on chromosome 21,[3] and genetic mutations of APP was found in the patients with early-onset familial AD. The hypothesis was further studied by Hardy and Higgings[1] in 1992 and has been revised and updated on several occasions since then.[4]

During the 1990s, the proteolytic processing of APP was newly known. Several mutations related to the disease in sites within APP that are normally cleaved by a series of proteases were identified as α-, β-, and γ-secretases.[5] Aβ generation depended on APP proteolytic cleavage by β- and γ -secretases.[6,7] These serial observations formed the amyloid cascade hypothesis.

The pathological process involving the formation of neurofibrillary tangles containing tau protein, is thought to result from an imbalance between production and clearance of Aβ.[8] Therefore, to find the mechanism leading to Aβ degeneration from APP is important. APP is a single-pass transmembrane protein with a large extracellular domain and containing 770 amino acids. Though this is widely expressed in neurons, its physiological function has yet to be fully understood.[8] In amyloid cascade hypothesis, APP may be processed by either the non-amyloidogenic or the amyloidogenic pathway.

The most of APP processing follows the non-amyloidogenic pathway and involves α-secretase. This cleaves APP 83 amino acids from the C-terminus, resulting in an N-terminal fragment that is secreted into the extracellular domain (sAPP α) and a C-terminal fragment of 83 amino acids (C83); the latter remains associated with the membrane and subsequently cleaved by γ -secretase, yielding a short soluble peptide (p3). In the amyloidogenic pathway, however, APP is first cleaved by β-secretase at the position 99 amino acids from the C-terminus. This generates a secreted extracellular domain (sAPPβ) and a membrane-associated C-terminal fragment containing 99 amino acids (C99). C99 is cleaved by γ -secretase at different locations, releasing A β, which contains between 37 and 49 amino acids (A β 37-A β 49); Aβ 40 and Aβ 42 (more hydrophobic than Aβ 40) are major components of the accumulated Aβ.

The amyloid cascade hypothesis postulated that an increase in the extracellular level of Aβ 42 or an increase in the ratio of Aβ 42 generate and promote Aβ amyloid fibril formation, and the accumulated Aβ amyloid fibrils result in senile plaque, which cause neurotoxicity and lead to neuronal damage. In summary, the amyloid dysregulation is the primary factor for development of AD.[9,10]

Vascular Hypothesis of Alzheimer's Disease

In 1993, de la Torre and Mussivand found reduced cerebral blood flow, glucose metabolism, and oxygen consumption in patients with AD and these reductions was proportional to disease severity. According to these observations, they propose the vascular hypothesis of AD.[11]

The vascular hypothesis of AD is an alternative to the amyloid cascade hypothesis for explaining the pathogenesis of AD. Cerebrovascular dysfunction and vascular pathology primary contribute to cognitive dysfunction and neuronal damage in AD.[12] Numerous evidences show that AD is associated with and this may be more than simple association of comorbid vascular lesion. Many studies from epidemiology, pharmacology, neuroimaging, clinical medicine, microscopic anatomy, and cellular-molecular biology also strongly suggest that sporadic AD is a vascular disorder.

Today, increasing evidence for vascular dysfunction role in AD development support the vascular hypothesis. Contrary to amyloid cascade hypothesis, senile plaque and neurofibrillary tangles may be the result, rather than the cause, of neurodegeneration. The two-hit vascular hypothesis of AD, damage to blood vessels is the initial insult, causing blood-brain barrier (BBB) dysfunction and diminished brain perfusion that, in turn, lead to neuronal injury and Aβ accumulation in the brain.[12,13] Several cerebrovascular dysfunctions might act independently and synergistically with Aβ to generate and propagate AD pathology, which is accelerated by genetic risk factors [such as carriage of the E4 allele of apolipoprotein E (APOE ε4)] and environmental risk factors (such as pollution).[13,14]

Similar pathology have been also found in the patients with traumatic brain injury, where APP overexpression and amyloid deposition seen in brain of patients with AD may occur during the acute stage of neuronal injury.[15] Moreover, the degree of Aβ deposition does not seem be correlated with the severity of cognitive dysfunction in patients with AD. In fact, amyloid deposition has also been found in the brains healthy elderly without cognitive dysfunction.[16]

Epidemiological studies of vascular risk factors and Alzheimer's Disease

Many studies showed that vascular risk factors were associated with an increased risk of developing AD. Arterial hypertension in elderly people who had never taken medications,[17] systolic hypertension and high serum cholesterol levels in middle-aged people increased the risk of development AD later in life.[18] The obesity and overweight in middle age were also independently increased risk of development AD.[19] Insulin resistance is one of the main obesity-linked risk factors and it also increase the risk of AD.[20] Atherosclerosis is another independent risk factor in development of AD. Hofman et al.[21] reported that patients with atherosclerosis were three times more likely to develop AD.

Neurovascular unit dysfunction in Alzheimer's disease

Cerebral microvascular endothelium, astrocytes, pericytes, neurons, and the extracellular matrix constitute the functional unit, so called neurovascular unit. These different types of cells control the vascular and neuronal inter-transport. Vascular cells (endothelial cells and pericytes) may directly affect neuronal and synaptic function by changing permeability of the BBB, blood flow, nutrient supply, clearance of toxic substances, secretion of trophic factors and matrix molecules, and induction of diverse receptors.[22]

Endothelial damage leads to breach of tight junction, which increase uncontrolled trans-endothelial flow.[12,13] The associated pericyte degeneration also causes BBB breakdown[23] and trigger diverse neurodegeneration owing to the entry of blood-derived toxic molecules such as plasminogen, thrombin and fi-

brinogen. Considering the BBB's major role in controlling the entry of systemic blood metabolites to brain tissue, breach of BBB may have exposed the neurotoxic molecules in the vulnerable brain. The increasing evidences of BBB dysfunction have been shown in AD, leading to BBB permeability alterations. Tight junction proteins and some extracellular matrix proteins are substrates for matrix metalloproteinase (MMP). High expression of MMP and the alterations on BBB permeability in AD suggested the degradation of these.[12] Alteration of BBB permeability may also affect selective transport. Selective transport molecules transport the certain circulating molecules to the brain through the blood. Mooradian et al.[24] reported low sodium-independent glucose transporters (GLUT-1; facilitated transporters) concentrations in the brain tissue of patients with AD; these low GLUT-1 expression may reflect the reduced glucose transport from blood to the brain and the decrease in the substrates necessary for adequate neuronal function.

The BBB has certain role in the regulation of Aβ levels in the brain. In fact, peripheral Aβ is an important precursor of central Aβ. The receptor for advanced glycation end-products (RAGE) manage Aβ transport to the brain. High RAGE expression in brain means increased influx transport of Aβ across the BBB and the consequent toxicity of Aβ.[12] In animal model of AD, RAGE expression proportionally increases as the disease progress and Aβ pathologic propagation.[25]

On the other hand, several animal studies of AD and patients with AD have shown decreased Aβ degradation in brain.[26,27] In Aβ degradation, cell surface receptor LRP1 has major role.[28] Low levels of low-density lipoprotein receptor-related protein 1 (LRP1) in brain vessels are associated with Aβ accumulation in the brain during aging and AD.[29] In patients with AD, brain LRP1 has also been known to be metabolized by means of an oxidative mechanism that may involve Aβ itself. This process results in Aβ deposition given that the oxidative form of LRP1 cannot efflux Aβ.[30] Finally, APOE ε 4, unlike APOE ε 3 and APOE ε 2, has been known block LRP1-mediated transport of Aβ from the brain, thereby it facilitates Aβ accumulation in brain.[31] APOE, LRP1, and cholesterol metabolism may be associated with Aβ in brain.[32]

Cerebral blood flow dysfunction in Alzheimer's disease

Cerebral blood flow dysfunctions such as decreased blood vessel atrophy, microvascular density, increased capillary irregularity, blood vessel diameter change, and increased thickness of basement membrane was found in patients with AD.[33] These cerebral blood flow insufficiency may cause neurodegenerative lesions such as senile plaques or neurofibrillary tangles.[34,35]

Hypoxia, which results from cerebral blood flow insufficiency, increase the expression of hypoxia-inducible factor 1 α (HIF-1 α) in neurons. HIF-1 α binds to the hypoxia-sensitive element of the gene coding for β-secretase, thereby increase the expression of β-secretase mARN and production of Aβ fragments.[36] In addition, hypoperfusion may lead to oxygen deficiencies which result in neuroglial metabolic stress; this will increase Aβ production and the generation of mitochondrial reactive oxygen species (ROS).[37] These serial events may suggest the molecular mechanisms underlying the accelerated Aβ deposition due to chronic cerebral hypoxia.[38]

Aβ interacts with the RAGE receptor on the blood vessel wall and this result in Aβ into the brain parenchyma. Aβ also promotes the production of endothelin-1, a vasoconstrictor peptide derived from the endothelium and this may also alter cerebral blood flow.[39]

In summary, cerebral hypoperfusion induce Aβ accumulation in the brain, and Aβ accumulation in turn aggravates vascular disease. Vascular disease may act in synergy with changes in Aβ levels through a positive feedback system in which tissue damage caused by vascular factors may increase neurodegenerative damage, and vice versa.

Microbleeds in AD

Damage to blood vessels can manifest as cerebral microbleeds (microhaemorrhages), which are frequently seen in AD,[40] MCI and in APOE ε4-positive individuals (who have an increased genetic risk of AD).[41] Cerebral amyloid angiopathy (CAA) is one of the main causes of vascular degeneration and lobar microbleeds in AD and contributes to BBB breakdown, infarcts, white matter changes and cognitive impairment.[22] Microbleeds in AD are predominantly lobar (similar to CAA-associated microbleeds) and are mainly found in the occipital lobe.[42]

Inflammation, vascular dysfunction, and Alzheimer disease

Alterations in cerebrovascular metabolic functions may also trigger multiple inflammatory factors. Cerebral vessels of patients with AD show higher levels of tumor necrosis factor- α (TNF- α) interleukin-1β (IL-1β), IL-6, chemokines (CCL2 and IL-8), MMP, and leucocyte adhesion molecules than controls do.[43] These inflammatory mediators can regulate Aβ production. Stimulating astrocytes using such inflammatory cytokines as TNF- α and interferon- γ (INF- γ) increased Aβ secretion and the levels of APP and -secretase.[44] These inflammatory changes may be associated with pathogenetic mechanisms of AD

Treatment Perspectives to Alzheimer's Disease Based on Vascular Hypothesis

Considering current evidence that the vascular dysfunction play an important role in AD development, vascular drugs such as non-steroidal anti-inflammatory drugs (NSAID), statins, and anti-hypertensive drugs may be promising candidates for the prevention and treatment of AD.[45]

In several retrospective epidemiological studies, NSAIDs significantly reduce the risk of developing AD.[46,47] These findings are also shown from animal studies of AD, which suggest the anti-inflammatory drug reduces Aβ deposition in the brain.[48] However, prospective clinical trials of NSAIDs have failed for therapeutic benefits.[49,50] Why these discrepancies occur are not clear. One possible explanation is that epidemiological studies recruit patients whose clinical manifestations are not yet evident, whereas clinical studies recruit patients whose clinical manifestations are clinically evident. Once the clinical symptoms occur, the pathologic processing may progress regardless of intervention. Another possible explanation is problems of drug selection and optimization. Given the wide range of anti-inflammatory drugs and the differences in their pharmacological activity, these are critical in clinical trials. To achieve this aim, better understanding of the mechanisms involved in the inflammatory processes contributing to AD progression is important.[51]

In experimental studies with animal models, statin have provided evidence of prevention senile plaque formation. However, clinical prospective statins trials for AD prevention and treatment have no significant benefits.[52,53] A similar hypothesis suggests that clinical trials may have been conducted in patients whose clinical manifestations are clinically evident, these patients may be too late for intervention, when damage was already irreversible or there was nothing left to preserve. They may have already missed the window of opportunity.

In antihypertensive treatment, a clinical trial showed that use of antihypertensive drugs was associated with lower incidence of dementia.[54] More specifically, Yasar et al.[55] showed that use of diuretics, angiotensin-1 receptor blockers, and angiotensin-converting enzyme inhibitors was associated with a lower risk of developing AD in cognitively healthy patients. In patients with mild cognitive impairment, however, only use of diuretics was associated with lower risk of AD. Whether antihypertensive drugs are suitable for treating AD is still under debate; further prospective clinical trials are necessary to answer the true therapeutic value of these drugs.[56]

Conclusion

Over decades, AD is considered as primary neuronal origin and underlying vascular disease is secondary to neurodegeneration. Contrast this traditional concept, the vascular hypothesis of AD suggests that various pathogenic pathways related with brain blood vessels may be the primary and initial triggering factors. In any case, cumulating evidences suggest that vascular disease and neurodegenerative changes acts synergistically each other, which results in greater cognitive decline.

Still now, whether the vascular dysfunction in AD is the cause or rather the effect of the disease is difficult to be clearly determined. Nonetheless, the role of vascular dysfunction is important in AD pathogenesis. BBB disruption and decreased cerebral blood flow constitute the main vascular risk factors and neurodegeneration. BBB disruption facilitate Aβ deposition and decreases the clearance Aβ deposition. On the other hand, cerebral blood flow decrease cause APP expression and β-secretase activity increase, in turn, which results in Aβ accumulation. From this point, cerebral hypoperfusion would favor Aβ deposition by means of a positive feedback mechanism; Aβ accumulation, in turn, would aggravate vascular dysfunction, causing inflammation and oxidative stress. This would accelerate neurodegeneration and cause the cognitive deficits typical of AD.

Elucidating the impact of the vascular system on AD pathogenesis helps broaden our horizon on therapeutic approaches and perspective on AD treatment options. Studying this idea is therefore essential in clarifying the pathophysiology of AD.

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