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The Role of Vascular Dysfunction in Alzheimer's Disease and Therapeutic Potential of Small Extracellular Vesicles

Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disorder that has long been characterized by the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles, leading to neuronal loss and cognitive decline. These hallmark features have been the primary focus of AD research for decades. However, a growing body of evidence suggests that vascular dysfunction may play a crucial and potentially initiating role in AD pathogenesis. This shift in perspective has opened up new avenues for understanding the disease and developing potential treatments.[1,2,3]

This essay explores the hypothesis that vascular impairment, particularly endothelial cell dysfunction, contributes significantly to the onset and progression of AD. We will examine how this vascular dysfunction interacts with other pathological processes, creating a cascade of events that results in Aβ accumulation, tau hyperphosphorylation, and further vascular deterioration. By delving into the intricate relationships between vascular health and neurodegeneration, we aim to provide a comprehensive overview of this emerging field of study.

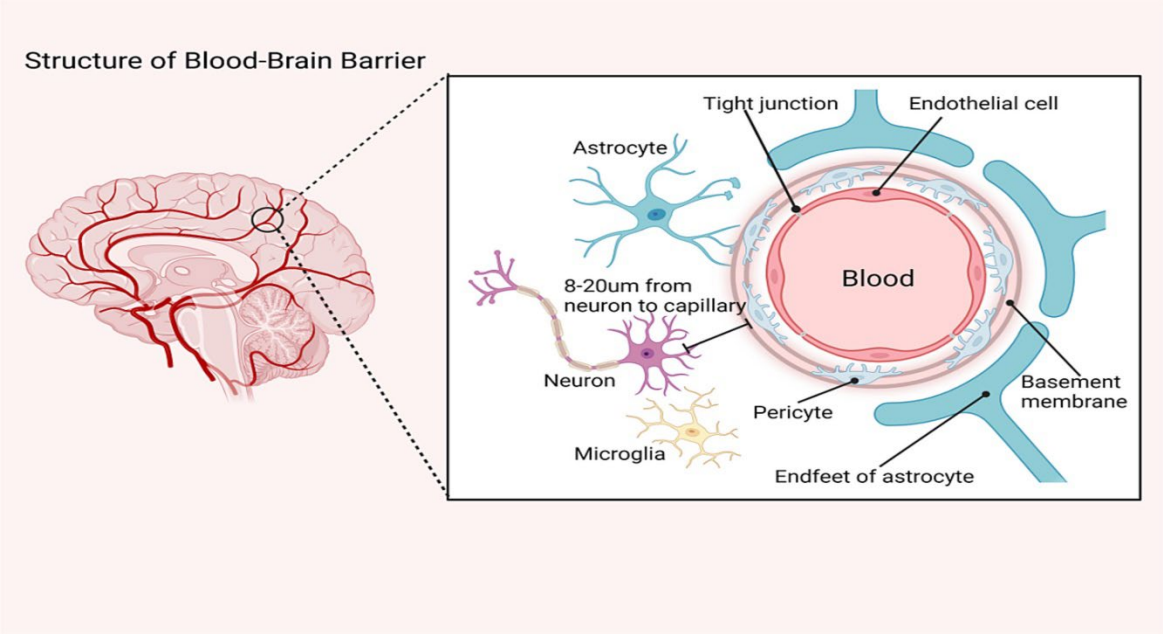
The following sections will explore the concept of the neurovascular unit and its role in AD, the central importance of endothelial cell dysfunction, the regional heterogeneity of brain vasculature and its implications for disease progression, the influence of neuropathological factors on endothelial dysfunction, the temporal dynamics and feedback loops in AD progression, the consequences of impaired neurovascular coupling,
and the therapeutic Potential of exosomes derived from young donors in Alzheimer's Disease in the context of the vascular hypothesis. Through this exploration, we hope to shed light on the complex interplay of factors contributing to AD and point towards promising directions for future research and treatment strategies.

The Neurovascular Unit as a Central Player in AD

The neurovascular unit (NVU) is a fundamental concept in understanding how vascular dysfunction contributes to AD. This intricate system comprises multiple cell types and structures working in concert to maintain brain health. The NVU consists of endothelial cells that line the blood vessels, forming the critical interface between the bloodstream and brain tissue. Surrounding these endothelial cells are pericytes, which wrap around the vessels and play a crucial role in regulating blood flow and maintaining vascular stability. Astrocytes, with their characteristic star-shaped morphology, extend end-feet that envelop the blood vessels, contributing to the blood-brain barrier (BBB) and facilitating communication between neurons and the vasculature. Neurons, the primary functional units of the brain, are intimately connected to this vascular network, relying on it for oxygen and nutrients. The extracellular matrix,

composed of various proteins and proteoglycans, provides structural support and contributes to signaling within the NVU.

In healthy brain tissue, the NVU performs several critical functions. It maintains the integrity of the BBB, a selective barrier that tightly regulates the passage of substances between the bloodstream and the brain parenchyma. This barrier is crucial for protecting the brain from potentially harmful blood-borne substances while allowing the passage of essential nutrients. The NVU also plays a vital role in regulating cerebral blood flow (CBF), ensuring that neurons receive an adequate supply of oxygen and glucose to meet their high metabolic demands. Additionally, the NVU facilitates the clearance of metabolic waste products from the brain, a process that is increasingly recognized as crucial for maintaining cognitive health.[4]



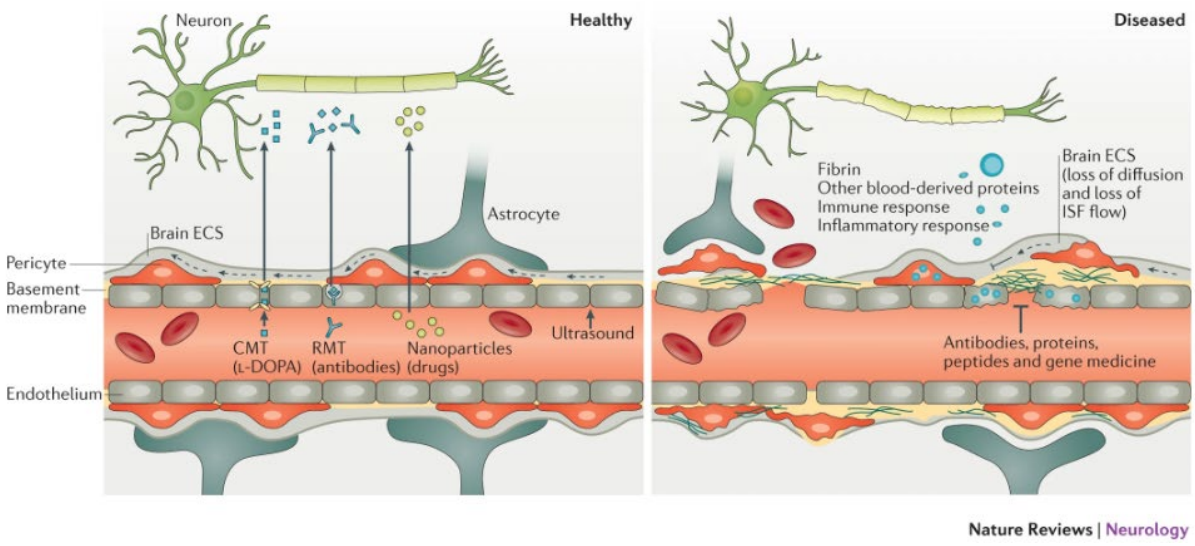
Emerging research indicates that disruptions in the NVU, particularly endothelial cell dysfunction, may represent early pathological events in AD. Impaired cerebral blood flow is often observed before the appearance of Aβ plaques and cognitive symptoms, suggesting that vascular abnormalities may precede and potentially trigger the accumulation of neurotoxic proteins. This initial vascular dysfunction can lead to a cascade of detrimental effects in brain tissue.[5]

One of the primary consequences of early vascular dysfunction is hypoperfusion, a state of reduced blood flow that results in inadequate oxygen and nutrient delivery to brain tissues. This state of hypoperfusion can lead to localized hypoxia, where cells are deprived of sufficient oxygen to maintain optimal function. In response to this oxygen deprivation, cells may increase the production of reactive oxygen species, leading to elevated levels of oxidative stress. This oxidative environment can damage cellular components, including proteins, lipids, and DNA, further compromising cellular function.

The metabolic deficits resulting from hypoperfusion and hypoxia create an environment that is conducive to AD pathology. Research has shown that hypoxic conditions can upregulate the expression of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), an enzyme involved in the production of Aβ. While the exact mechanism and extent of this upregulation in

human AD are still subjects of ongoing research, this finding suggests a potential link between vascular dysfunction and increased Aβ production. Furthermore, the oxidative stress induced by hypoxia may activate various kinases, including glycogen synthase kinase-3β (GSK-3β), which has been implicated in promoting tau hyperphosphorylation. Although this pathway is plausible and supported by some experimental evidence, more research is needed to fully elucidate its role in human AD pathogenesis.[6,7]

Another critical aspect of early vascular impairment in AD is the breakdown of the blood-brain barrier. A compromised BBB can have far-reaching consequences for brain health. When the BBB becomes leaky, it allows neurotoxic blood-derived molecules, proteins, and immune cells to infiltrate the brain parenchyma. This infiltration can trigger and exacerbate neuroinflammation, a process increasingly recognized as a significant contributor to AD pathology. The presence of these blood-derived elements in the brain can also directly contribute to neuronal damage, further accelerating the neurodegenerative process.



Moreover, BBB dysfunction can impair the clearance of Aβ and tau proteins from the brain. Under normal conditions, the BBB plays a crucial role in removing these potentially harmful proteins from the brain parenchyma. When this clearance mechanism is compromised, it can facilitate the accumulation and aggregation of Aβ and tau, two hallmark pathologies of AD. This accumulation can, in turn, further damage the vasculature, creating a vicious cycle of vascular dysfunction and protein aggregation.

These processes collectively initiate a feedback loop wherein vascular impairment accelerates neurodegeneration, which in turn exacerbates vascular dysfunction. Understanding this complex interplay between vascular health and neurodegeneration is crucial for developing a comprehensive view of AD pathogenesis and identifying potential points of intervention in the disease process.[8,9]

Endothelial Cell Dysfunction as a Catalyst

Endothelial cells play a central and multifaceted role in maintaining vascular homeostasis. In healthy conditions, these cells form the innermost lining of blood vessels and perform a variety of critical functions. One of their primary roles is the production of nitric oxide (NO), a potent

vasodilator that helps regulate vascular tone and blood flow. NO not only promotes vasodilation but also has anti-inflammatory and antithrombotic properties, contributing to overall vascular health.

Beyond NO production, endothelial cells are crucial in regulating vascular tone and blood flow through other mechanisms. They respond to various chemical and mechanical stimuli, adjusting vessel diameter to meet the metabolic demands of surrounding tissues. This ability to dynamically regulate blood flow is particularly important in the brain, where energy demands can change rapidly based on neuronal activity.

Endothelial cells are also the primary components of the blood-brain barrier. They form tight junctions with one another, creating a highly selective barrier that tightly controls the passage of substances between the bloodstream and the brain parenchyma. This barrier function is essential for maintaining the unique microenvironment required for proper neuronal function.

Furthermore, endothelial cells express a variety of transporters and receptors involved in nutrient delivery and waste removal. These include glucose transporters, amino acid carriers, and efflux pumps that help maintain the delicate balance of substances in the brain. The proper functioning of these transport systems is crucial for brain health and cognitive function.[10]

Aging is significant factor that contributes to endothelial dysfunction. As individuals age, their endothelial cells become less efficient at producing NO and are more susceptible to oxidative stress. This age-related decline in endothelial function may partly explain the increased risk of AD in older populations.[11]

Certain lifestyle choices can also have a profound impact on endothelial health. Smoking, for instance, exposes endothelial cells to a host of toxic substances that can cause direct damage and impair their function. A sedentary lifestyle is associated with reduced shear stress on blood vessels, which can lead to endothelial dysfunction over time. Conversely, regular physical activity has been shown to improve endothelial function and may be protective against cognitive decline.[12,13]

When endothelial cells become dysfunctional, several detrimental effects occur. The reduced production of NO leads to impaired vasodilation and a shift towards a more vasoconstricted state. This results in decreased cerebral blood flow, which can have significant consequences for brain health. The brain, with its high metabolic demands, is particularly sensitive to reductions in blood flow. Even mild, chronic hypoperfusion can lead to neuronal stress and eventual neurodegeneration.

Endothelial dysfunction is also associated with increased oxidative stress. Dysfunctional endothelial cells produce more reactive oxygen species and have a reduced capacity to neutralize these harmful molecules. This oxidative environment can damage surrounding tissues, including neurons and glial cells, contributing to the progression of neurodegenerative processes.

The impairment of neurovascular coupling is another significant consequence of endothelial dysfunction. Neurovascular coupling refers to the tight relationship between neuronal activity and local blood flow. In a healthy brain, increased neuronal activity leads to a rapid and localized increase in blood flow to meet the heightened metabolic demands. When endothelial cells are dysfunctional, this coupling mechanism becomes impaired, leading to a mismatch

between neuronal activity and blood supply. This mismatch can result in periods of relative hypoxia and metabolic stress for neurons, potentially contributing to cognitive impairment and neurodegeneration.

The resulting hypoperfusion from endothelial dysfunction can exacerbate neuronal energy deficits, potentially promoting Aβ overproduction and tau hyperphosphorylation. The brain's attempt to compensate for reduced energy availability may lead to increased amyloidogenic processing of amyloid precursor protein, resulting in greater Aβ production. Similarly, energy deficits can activate kinases that promote tau hyperphosphorylation, a key step in the formation of neurofibrillary tangles.[14]

Moreover, Aβ peptides can directly injure endothelial cells by inducing oxidative stress and inflammatory responses, further impairing endothelial function. This creates a vicious cycle where endothelial dysfunction leads to Aβ accumulation, which in turn worsens vascular health. Breaking this cycle represents a potential therapeutic target in AD.[15]

Endothelial dysfunction also affects the expression of transporters and receptors involved in clearing Aβ and tau from the brain. For example, the expression of low-density lipoprotein receptor-related protein 1 (LRP1) on endothelial cells is often reduced in AD. LRP1 plays a crucial role in Aβ efflux from the brain to the bloodstream. Its reduced expression impedes Aβ clearance, increasing its cerebral accumulation and potentially accelerating the formation of amyloid plaques.[16,17]

Furthermore, impaired insulin signaling in endothelial cells, which can occur as a result of endothelial dysfunction, affects glucose metabolism and may influence tau phosphorylation. This link between metabolic disturbances and tau pathology underscores the complex interplay between vascular health, metabolism, and the hallmark pathologies of AD.[18]

In summary, endothelial cell dysfunction serves as a critical catalyst in the pathogenesis of AD, initiating and exacerbating a cascade of events that contribute to neurodegeneration and cognitive decline. Understanding the central role of endothelial health opens up new avenues for therapeutic interventions aimed at preventing or slowing the progression of AD.

Regional Heterogeneity and Differential Vulnerability

Recent advancements in single-cell sequencing technologies have revealed a fascinating aspect of brain vasculature: brain endothelial cells exhibit distinct transcriptional profiles based on their location within the brain. This regional heterogeneity has important implications for AD pathology and helps explain why certain brain areas may be more susceptible to initial vascular dysfunction and subsequent AD pathology.[19]

The concept of regional heterogeneity in brain vasculature challenges the notion of a uniform vascular system throughout the brain. Instead, it suggests that endothelial cells in different brain regions have unique molecular signatures that reflect their specialized functions and adaptations to local tissue environments. These distinct profiles can influence various aspects of vascular function, including barrier properties, transport mechanisms, and responses to stress or injury.

One of the key implications of this heterogeneity is that certain brain areas may be inherently more vulnerable to vascular insults. Regions with endothelial cells that have lower antioxidant capacity, for instance, may be more susceptible to oxidative stress-induced damage. Similarly,

areas with higher metabolic demands may be particularly sensitive to reductions in blood flow, making them more prone to hypoxia and energy deficits in the face of vascular dysfunction.

The hippocampus, a region critical for memory formation and one of the first areas affected in AD, serves as an excellent example of how regional vascular properties can influence disease vulnerability. Research has shown that the hippocampus has several unique vascular characteristics that may contribute to its early involvement in AD pathology.

Firstly, the hippocampus has a higher vascular density compared to many other brain regions. While this rich vascular network is crucial for supporting the high metabolic demands of hippocampal neurons, it also means that any systemic vascular dysfunction may have a more pronounced effect in this region. The greater surface area of vasculature in the hippocampus could potentially expose it to higher levels of circulating harmful substances or inflammatory mediators in the context of a compromised blood-brain barrier.

Secondly, endothelial cells in the hippocampus have been found to have distinct molecular signatures. Studies have identified genes that are differentially expressed in hippocampal endothelial cells compared to those in other brain regions. Some of these genes are involved in angiogenesis, vascular remodeling, and responses to hypoxia. This unique genetic profile may make hippocampal vessels more responsive to certain stimuli but potentially more vulnerable to specific types of vascular stress.[20]

Furthermore, the hippocampus appears to be particularly sensitive to reductions in blood flow. This sensitivity is likely due to its complex cellular architecture and the high energy demands of processes involved in memory formation and consolidation. Even mild chronic hypoperfusion can lead to significant functional impairments in the hippocampus, potentially explaining why memory deficits are often among the earliest cognitive symptoms in AD.[21]

The regional vulnerability extends beyond the hippocampus. Other brain areas, such as the prefrontal cortex and certain subcortical regions, also show early involvement in AD and may have unique vascular properties that contribute to their susceptibility. For example, the prefrontal cortex, crucial for executive functions and often affected in AD, has a complex vascular architecture that may make it particularly sensitive to changes in blood flow and BBB integrity.[22]

Understanding these regional differences in vascular biology is crucial for several reasons. First, it helps explain the pattern of neurodegeneration observed in AD, where certain brain areas are affected earlier and more severely than others. This knowledge can inform early diagnostic strategies, potentially allowing for the identification of at-risk individuals before widespread neurodegeneration occurs.

Secondly, recognizing regional vascular heterogeneity can guide the development of more targeted therapeutic approaches. Treatments could be designed to address the specific vulnerabilities of endothelial cells in AD-prone regions. For instance, if hippocampal vessels are found to be particularly sensitive to oxidative stress, antioxidant therapies could be developed that specifically target or accumulate in this region.

Lastly, this concept of regional heterogeneity underscores the importance of studying AD from a systems perspective. While much research has focused on specific molecular pathways or individual cell types, understanding how different brain regions and cell populations interact and

influence each other's vulnerability to disease processes is crucial for developing a comprehensive view of AD pathogenesis.

In conclusion, the regional heterogeneity of brain vasculature adds another layer of complexity to our understanding of AD. It highlights the need for nuanced approaches in both research and treatment strategies, taking into account the unique properties of different brain regions and their vasculature. As research in this area progresses, it may lead to more precise and effective interventions for preventing and treating AD.

Influence of Neuropathological Factors on Endothelial Dysfunction

While initial vascular impairment may precede other AD pathologies, it is crucial to recognize that factors such as Aβ deposition, tau pathology, and APOE genotype can further exacerbate endothelial dysfunction. This creates a complex interplay where vascular issues both contribute to and are aggravated by the classic pathological hallmarks of AD.

Aβ accumulation, particularly in cerebral vessels as seen in cerebral amyloid angiopathy (CAA), has profound effects on vascular health. As Aβ deposits in the walls of blood vessels, it leads to vascular stiffening and reduced elasticity. This loss of vascular flexibility impairs the ability of blood vessels to respond appropriately to changes in metabolic demand, further compromising cerebral blood flow regulation.[23]

At a molecular level, Aβ interacts directly with endothelial cells through various receptors, triggering a cascade of detrimental effects. These interactions can induce apoptotic pathways, leading to endothelial cell death and breakdown of the BBB. Additionally, Aβ triggers inflammatory responses in endothelial cells, promoting the release of pro-inflammatory cytokines and increasing the expression of adhesion molecules. This inflammatory state not only damages the endothelial cells themselves but also attracts immune cells, further exacerbating local inflammation and vascular damage.[24]

The integrity of tight junctions between endothelial cells, crucial for maintaining BBB function, is also compromised by Aβ. This breakdown in BBB integrity allows for increased penetration of potentially harmful substances into the brain parenchyma and impairs the clearance of metabolic waste products, creating a neurotoxic environment that accelerates neurodegeneration.

Tau pathology, another hallmark of AD, also plays a significant role in vascular dysfunction. While traditionally viewed primarily as an intraneuronal pathology, recent research has highlighted important interactions between tau and the vascular system. Hyperphosphorylated tau can impair the neuronal support of endothelial cells, disrupting the delicate balance of the neurovascular unit.[25]

In healthy conditions, neurons provide trophic support to endothelial cells and help regulate vascular function through various signaling pathways. As tau becomes hyperphosphorylated and aggregates into neurofibrillary tangles, this support is compromised. The resulting dysfunction in neurovascular coupling can lead to inadequate blood flow responses to neuronal activity, creating periods of relative hypoxia and metabolic stress.

Moreover, there is growing evidence that tau aggregates may not be confined to neurons. Extracellular tau, released from dying or stressed neurons, can interact directly with endothelial cells. These interactions may alter endothelial cell function, affecting vascular tone and BBB

maintenance. Some studies have suggested that tau may even be capable of propagating from cell to cell, raising the possibility that vascular cells could be directly affected by spreading tau pathology.[26]

The APOE genotype, particularly the APOE4 allele, is the strongest genetic risk factor for late-onset AD and has been linked to inherent endothelial dysfunction. Individuals carrying the APOE4 allele may experience earlier onset of vascular dysfunction, potentially setting the stage for subsequent Aβ accumulation and tau hyperphosphorylation.

APOE4 affects endothelial function through multiple mechanisms. It alters lipid metabolism in endothelial cells, potentially affecting membrane composition and fluidity. This can impact the function of membrane-bound receptors and transporters crucial for maintaining vascular health and BBB integrity. APOE4 also influences inflammatory responses in the vasculature, with carriers showing increased markers of vascular inflammation even in the absence of overt cognitive impairment.

Furthermore, APOE4 has been associated with reduced glucose uptake in the brain, which may be partly due to its effects on vascular function. Impaired glucose metabolism can lead to energy deficits in neurons, potentially accelerating neurodegenerative processes. The combination of APOE4-related vascular dysfunction and metabolic disturbances may create a particularly vulnerable environment for AD pathogenesis.

It's important to note that while APOE4 increases the risk of AD, it is neither necessary nor sufficient for developing the disease. Many individuals with the APOE4 allele never develop AD, while others without this genetic variant do. This underscores the complex, multifactorial nature of AD and highlights the potential for other genetic and environmental factors to modulate disease risk.[27,28]

The interplay between these neuropathological factors and vascular dysfunction creates a complex, self-reinforcing cycle in AD. Initial vascular impairment may facilitate the accumulation of Aβ and the spread of tau pathology. In turn, these pathologies further damage the vasculature, exacerbating the initial dysfunction. Understanding these interactions is crucial for developing comprehensive therapeutic strategies that address multiple aspects of AD pathology simultaneously.

Temporal Dynamics and Feedback Loops

The progression of Alzheimer's disease is characterized by complex temporal dynamics and feedback loops involving vascular dysfunction, Aβ accumulation, tau pathology, and neurodegeneration. Analyzing these relationships reveals a intricate interplay of factors that contribute to the relentless progression of the disease.

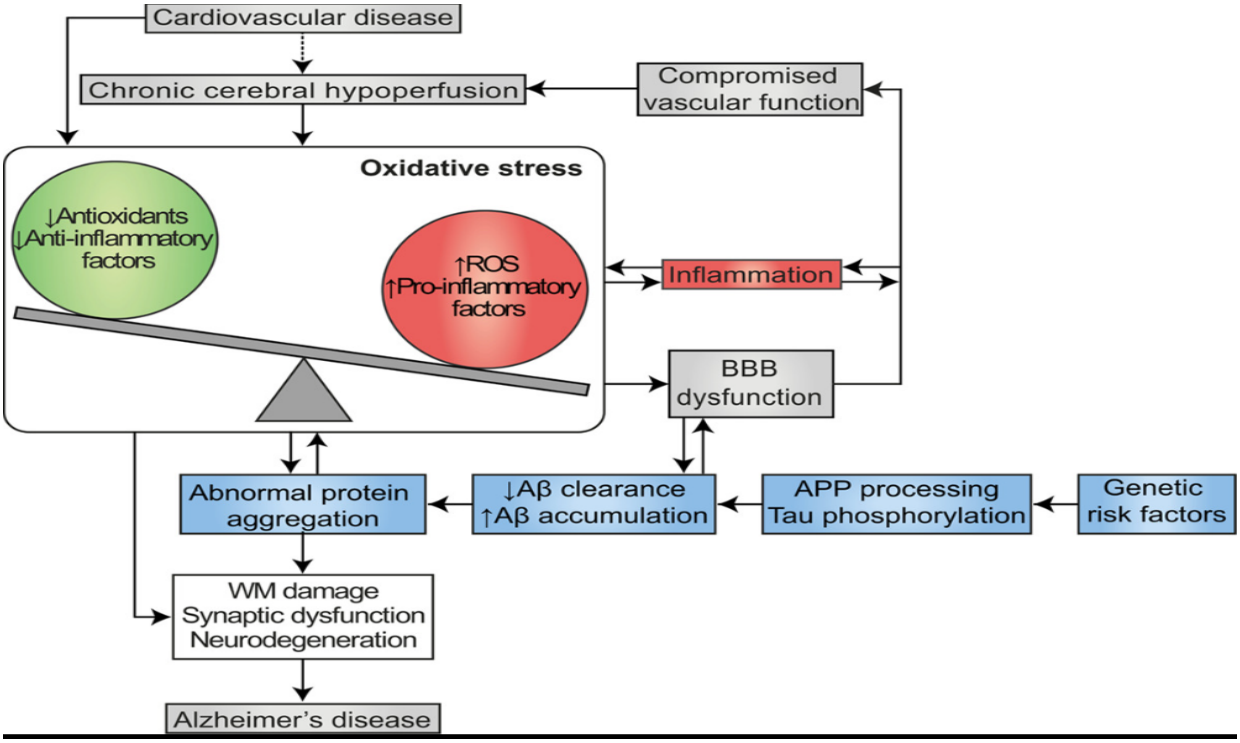
Early endothelial dysfunction, which may precede clinical symptoms by years or even decades, sets the stage for a cascade of pathological events. The initial vascular impairment leads to localized areas of hypoxia and increased oxidative stress in the brain tissue. These conditions create an environment that is conducive to the overproduction of Aβ and the hyperphosphorylation of tau protein.

As Aβ begins to accumulate, it exerts direct toxic effects on endothelial cells, further compromising vascular function. This creates a positive feedback loop where vascular dysfunction promotes Aβ production, and increased Aβ levels further damage the vasculature. Similarly, as tau becomes hyperphosphorylated and begins to aggregate, it can impair neurovascular coupling and directly interact with endothelial cells, exacerbating the initial vascular impairment.[29,30]

These processes do not occur in isolation but rather interact and amplify each other. For example, vascular-derived oxidative stress can promote both Aβ production and tau hyperphosphorylation. Conversely, both Aβ and tau can induce oxidative stress, creating a self-reinforcing cycle of cellular damage.

The temporal aspect of these interactions is crucial to understanding disease progression. While the exact sequence of events may vary between individuals, the general pattern suggests that vascular dysfunction occurs early in the disease process, possibly even before detectable Aβ accumulation or cognitive symptoms. This early vascular impairment may then accelerate the accumulation of AD pathology, which in turn further damages the vasculature.

As the disease progresses, these feedback loops become more pronounced. Increased levels of Aβ and tau pathology lead to neuronal dysfunction and death, which further impairs neurovascular coupling and exacerbates vascular dysfunction. This creates a downward spiral where each component of the disease process amplifies the others, leading to accelerating neurodegeneration and cognitive decline.



Courtesy Scheffer S, Hermkens DMA, van der Weerd L, de Vries HE, Daemen MJAP. Vascular Hypothesis of Alzheimer Disease: Topical Review of Mouse Models. Arterioscler Thromb Vasc Biol. 2021 Apr;41(4):1265-1283. doi: 10.1161/ATVBAHA.120.311911. Epub 2021 Feb 25. PMID: 33626911.

Understanding these temporal dynamics and feedback loops is crucial for identifying potential points of intervention in the disease process. Early interventions aimed at preserving vascular health may have the potential to slow or even prevent the accumulation of AD pathology. Similarly, therapies targeting Aβ or tau may need to consider their effects on vascular function to be maximally effective.

Moreover, this understanding highlights the need for combination therapies that address multiple aspects of AD pathology simultaneously. By targeting vascular health, Aβ accumulation, and tau pathology concurrently, it may be possible to interrupt the self-reinforcing cycles that drive disease progression.

Therapeutic Potential of Exosomes Derived from Young Donors in Alzheimer's Disease

As evidence continues to accumulate supporting the role of neurovascular dysfunction in Alzheimer’s disease (AD), the search for innovative therapeutic approaches has led researchers to investigate the potential of small extracellular vesicles, specifically exosomes, derived from young donors. Exosomes are circulating nanosized vesicles that are secreted by various cell types, that play a crucial role in intercellular communication. These vesicles transport proteins, lipids, and microRNAs (miRNAs) between cells, influencing a range of physiological processes. In the context of neurodegenerative diseases like AD, exosomes from young individuals have emerged as promising candidates for promoting neuroregeneration, neuroprotection, and reducing inflammation.[31]

Exosomes derived from young donors, typically aged 18-25, have shown compelling therapeutic potential for AD, offering a novel and targeted approach to addressing key aspects of the disease's pathology. Their protective effects can be attributed to several mechanisms, beginning with their ability to restore vascular health. Endothelial dysfunction is a key contributor to AD progression, leading to impaired cerebral blood flow and blood-brain barrier (BBB) breakdown. Exosomes from young endothelial cells are rich in bioactive molecules, including growth factors and miRNAs, that promote endothelial cell survival and function. For instance, exosomes from young donors contain miRNAs such as miR-126 and miR-210, which play important roles in angiogenesis and endothelial repair. These miRNAs enhance the production of nitric oxide (NO), a molecule essential for vasodilation and reducing oxidative stress. By restoring endothelial function, exosomes improve cerebral blood flow, reducing hypoperfusion and neurovascular uncoupling, which are critical components of AD pathology. Moreover, exosomes can help repair the BBB by strengthening the tight junctions between endothelial cells, thereby restoring its integrity. This repair process can prevent the infiltration of neurotoxic molecules and inflammatory cells into the brain, which are known to exacerbate neurodegeneration in AD. By enhancing BBB integrity, exosomes can also promote the clearance of amyloid-beta (Aβ) and tau proteins, which are key drivers of AD pathology.

In addition to vascular health, exosomes from young donors can modulate neuroinflammation, a critical factor in AD progression. Neuroinflammation in AD is driven by the activation of immune cells such as microglia and astrocytes in response to Aβ plaques and tau tangles. Exosomes derived from young donors carry miRNAs, such as miR-146a and miR-21, that suppress inflammation by inhibiting pro-inflammatory pathways like nuclear factor-kappa B (NF-κB) signaling. By reducing the levels of pro-inflammatory cytokines, these exosomes can help create a more favorable environment for neuronal survival. Furthermore, exosomes have been shown to influence microglial polarization, promoting a shift from the pro-inflammatory M1

phenotype to the anti-inflammatory M2 phenotype. This shift not only reduces neuroinflammation but also enhances the clearance of Aβ by microglia, thereby potentially slowing AD progression.[32,33,34]

Exosomes from young donors also hold promise for their neuroregenerative potential. In AD, neuronal loss and synaptic dysfunction are central to the cognitive decline experienced by patients. Exosomes derived from young individuals carry miRNAs such as miR-29b and miR-132, which support neuronal survival and synaptic plasticity. These miRNAs enhance the expression of synaptic proteins and activate neurotrophic pathways, such as those involving brain-derived neurotrophic factor (BDNF), which are critical for cognitive function. By promoting synaptic plasticity and protecting neurons from degeneration, exosomes may help preserve memory and cognition in AD patients. Moreover, these vesicles contain growth factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which stimulate neurogenesis in the hippocampus—a brain region significantly affected by AD. By promoting the generation of new neurons, exosomes may help compensate for neuronal loss, contributing to cognitive recovery.[35,36,37]

Another critical area in which exosomes may have therapeutic value is the clearance of toxic proteins associated with AD. Aβ and tau aggregates are hallmarks of the disease, and their accumulation drives neurodegeneration. Exosomes from young donors may facilitate the clearance of Aβ by delivering proteins such as neprilysin and insulin-degrading enzyme (IDE), which degrade Aβ. These exosomes can also upregulate the expression of low-density lipoprotein receptor-related protein 1 (LRP1) on endothelial cells, which is essential for the efflux of Aβ from the brain into the bloodstream. Through these mechanisms, exosomes can help reduce the cerebral accumulation of Aβ, slowing the progression of AD. Similarly, exosomes may promote the clearance of hyperphosphorylated tau by delivering autophagy-related proteins that facilitate the degradation of tau aggregates through lysosomal pathways. By enhancing both Aβ and tau clearance, exosomes address two of the primary drivers of AD pathology.38,39,40,41

In conclusion, exosomes derived from young donors represent a promising therapeutic strategy for Alzheimer’s disease. Their ability to restore vascular function, reduce neuroinflammation, promote neuroregeneration, and facilitate the clearance of toxic proteins provides a multifaceted approach to addressing AD pathology. Although preclinical studies have shown promising results, further research is required to optimize the isolation, delivery, and dosing of exosomes for clinical applications. As research in this area advances, exosome-based therapies could offer a novel and effective treatment for Alzheimer's disease, addressing both its vascular and neurodegenerative components.

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