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Mini Review

Neurovascular Unit Dysfunction in Dementia: A Brief Summary

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Abstract

Cerebral microvasculature constitutes a blood-brain interface that mediates the delivery of oxygen and nutrients into the brain and eliminates toxic metabolites from it. A functional blood-brain interface requires a dynamic and precise coordination between the cerebral microvasculature and parenchymal cells, including neurons, an aspect governed by the Neurovascular Unit (NVU). The NVU, which is constituted by vascular and non vascular cells, couples neuronal activity to vascular function, controls brain homeostasis and shapes brain's immune responses, thus consequently maintains an optimal brain microenvironment adequate for neuronal survival. Several new findings ignited interest in investigating the pathophysiology of the NVU in several brain disorders, namely dementia-related diseases such as Alzheimer's disease (AD) and vascular dementia (VaD). Recent reports and hypotheses suggested a central role of NVU dysfunction as a key component involved, not only in worsening and aggravating the pathology of AD and VaD, but also as an early mediator in initiating the complex process of neurodegenerative cascades observed in these disorders. Therefore, understanding the molecular and cellular mechanisms involved in NVU dysfunction would constitute an extraordinary tool to get better insights into the pathobiology of AD and VaD, which would consequently lead to the development of novel therapeutic approaches. In this manuscript, I will be summarizing the implication of NVU injury in AD and VaD pathogenesis development. Moreover, I will be highlighting the contribution of cerebral microcirculation impairment in triggering NVU injury at the early stages of both diseases and outlining new therapeutic avenues that emphasis on NVU repair.

Keywords: Neurovascular unit; Blood-brain barrier; Vascular dementia; Alzheimer's disease; Neurodegenerative cascades; Signal transduction

Abbreviations

NVU: Neurovascular Unit; AD: Alzheimer's disease; VaD: Vascular Dementia; Aβ: beta-Amyloid; BBB: Blood-Brain Barrier; ECM: Extracellular Matrix; CBF: Cerebral Blood Flow; CAA: Cerebral Amyloid Angiopathy; WM: White Matter; LRP1: Low-Density Lipoprotein (LDL) receptor 1; ABCB1: Adenosine Triphosphate (ATP) Binding Cassette Receptor B1; CD11b: Cluster of Differentiation 11b (CD11b); TLRs: Toll-Like Receptors (TLRs); HIF1α: Hypoxia-Inducible Factor 1α; IL1β: Interleukin 1β; LXR: Liver X receptor; PPARγ: Peroxisome Proliferator-Activated Receptor γ; NPCs: Neuronal Precursor Cells; MSCs: Mesenchymal Stem Cells.

Introduction

The proper function of the brain totally relies on the integrity of its vascular network. The cerebral microvasculature constitutes a blood-brain interface that acts as a functional bridge between the periphery and the brain [1]. Anatomically, at the luminal side of cerebral microvasculature that faces blood circulation, tightly sealed endothelial cells form a specialized barrier, the Blood-Brain Barrier (BBB), which controls brain homeostasis and microenvironment by adjusting nutrient and oxygen delivery into the brain, removing toxic metabolites from the brain, protecting the brain from circulating toxic molecules, limiting the uncontrolled entry of blood-borne immune cells into the brain and supporting neuronal viability [1]. In order to fulfill its role in maintaining brain homeostasis and microenvironment, the BBB is complemented by several sophisticated exchange and transport systems, such as ion channels, pumps and transporters [2]. In parallel, at the abluminal side of cerebral microvasculature that faces brain parenchyma, the BBB dynamically and actively interacts with Extracellular Matrix (ECM) proteins, pericytes, astrocytes, microglia and neurons, forming altogether the Neurovascular Unit (NVU) [3]. The NVU constitutes a functional unit that couples neuronal activity to vascular function by controlling regional Cerebral Blood Flow (CBF), and controls brain homeostasis by adjusting the parameters of the BBB. Moreover, the NVU plays a crucial role in shaping brain immune responses. Under physiological conditions, it maintains a tight control over the function and activity of microglia, which are brain resident macrophages [3,4]. Therefore, the proper function of the NVU is a prerequisite for a normal functioning of the brain, mainly by maintaining an optimal regional microenvironment adequate for neuronal function [5]. The physical and functional properties of the NVU are challenged in several brain disorders, among which are dementia-related diseases such as Alzheimer's disease (AD) and vascular dementia (VaD). Highlighting the contribution of NVU dysfunction in the pathobiology of these diseases and elucidating the pathological molecular and cellular

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mechanisms involved in this process constitute a great challenge that has to bet met in order to get better insights into disease development and to achieve efficacious therapeutic interventions.

Brain vascular pathologies in dementia: A Subtle interplay between causative factors and consequences

AD accounts up to 80% of dementia cases, thus constituting the most common form of dementia. It is a progressive neurodegenerative disorder that affects elderly persons, which begins with mild memory deficits that evolve over time to reach total cognitive impairment and loss of executive functions [6]. The formation of amyloid deposits, which is caused by beta-amyloid (Aβ) peptide oligomerization and aggregation, and neurofibrillary tangles, which is caused by hyperphosphorylated tau protein aggregation, are considered as the core pathological hallmarks of AD [6]. The pathogenesis of AD is highly associated to age. However, it is not exclusively related to physiological aging mechanisms, as small portion of the affected persons develop the disease early, translated by early onset symptoms that often appear at middle ages. Apart from the autosomal early onset familial form of AD, which accounts for up to 5% of the cases, the remaining majority has a sporadic late onset form [7]. It is still unknown how the sporadic form of AD develops, mainly due the heterogeneous factors involved in disease's development, such as aging and the complex interaction between several genetic and environmental factors. Therefore, the early events that initiate the neurodegenerative cascades observed in AD are still elusive. Nonetheless, the levels of toxic soluble cerebral Aβ have been shown to take place even before neurodegeneration [7]. This observation outlines the presence of early events that contribute in elevating the cerebral levels of toxic soluble Aβ. In the line with this observation, it has been reported that the toxic soluble Aβ accumulates at the early stages in cerebral vasculature, leading to the development of Cerebral Amyloid Angiopathy (CAA), which takes place in 80% of AD cases [8]. Interestingly, cerebrovascular dysfunction has been reported at the early stages of AD pathogenesis [9], outlining the possible contribution of brain vascular pathologies to AD development. In parallel, cerebrovascular dysfunction has been also documented in VaD, a group of heterogeneous brain disorders in which cognitive impairment is associated to preexisting pathologies in the brain vascular network [4]. VaD is responsible for at least 20% of cases of dementia, placing it as a second cause of dementia directly after AD [10]. The accurate causes leading to VaD are not fully elucidated. However, brain vascular pathologies associated to major focal strokes, mini-silent strokes, hypertension and heart attacks have been demonstrated to contribute to VaD development [3,4]. It is noteworthy here to mention that for anatomical reasons, White Matter (WM) is highly vulnerable to cerebrovascular dysfunction [11] and WM lesions have been shown to be tightly linked to chronic cerebral hypoperfusion, a form of cerebral microcirculation impairment associated to VaD pathogenesis [4]. Interestingly, AD and VaD coexist in many patients, a comorbidity that exacerbates the clinical outcomes of dementia [10]. This observation outlines overlapping mechanisms involved in the development of both diseases [4]. Indeed, several reports have suggested a central role of cerebral microcirculation impairments in triggering brain vascular pathologies and consequently contributing to AD and VaD pathogenesis development. More precisely, it has been reported that cerebral blood flow (CBF) chronic reduction, which deregulates glucose metabolism, occurs at the early stages of AD [12,13] and VaD [14]. Most importantly, cerebral microcirculation impairments have been suggested to take place even before cognitive decline [15]. This observation highlights the direct implication of cerebral microcirculation impairments in initiating the neurodegenerative cascades observed in AD and VaD. In parallel, several studies have shown the presence of several abnormalities at the BBB in AD [9] and VaD [16]. More precisely, the expression of the low-density lipoprotein (LDL) receptor 1 (LRP1) and the Adenosine Triphosphate (ATP) binding cassette receptor B1 (ABCB1), both of which have been demonstrated to be involved in cerebral Aβ elimination across the BBB [17,18]. Moreover, in a series of post-mortem brain tissue analysis, ABCB1 expression at the BBB was significantly decreased near Aβ plaques [19] and its expression was even absent at the BBB of CAA patients [20]. Similar to AD, abnormalities in the BBB has been reported in VaD. For example, VaD, induced by chronic cerebral hypoperfusion triggered NVU dysfunction, which was translated by a decrease in the expression of ABCB1 at the BBB [16]. Add on that, it has been reported that the physical integrity of the BBB is compromised in VaD associated disorders, such as Leukoaraiosis [21]. The function of the BBB constitutes a marker that reflects NVU health [5], thus these reports underline a direct pathological interactions between cerebral microcirculation impairments and NVU dysfunction, which are involved in AD and VaD pathogenesis development.

NVU injury in dementia: The translation of brain vascular pathologies

As mentioned, the NVU narrowly regulates brain's homeostasis and microenvironment [5]. The cerebral microcirculation has an intimate relationship with the NVU, deeply affecting its function. The NVU is a highly dynamic and flexible biological structure that possesses the capacity of remodeling as an attempt to adapt to a new physiological and/ or pathohysiological context [3,5]. This capacity is due to the highly dense and sophisticated biochemical signals that are evoked within the vicinity of the NVU, such as vasoactive molecules and neurotransmitters [4]. These signals contribute to the neurovascular coupling that bridges neuronal function to cerebral microcirculation. This coupling is translated by the adjustment of the regional CBF based on neuronal activity, needs and metabolic status [22]. This process requires a highly dynamic and synergistic interaction, and precise communication between the vascular (i.e. endothelial cells, pericytes) and non vascular (neurons, astrocytes and microglia) components of the NVU [22]. The acute non repetitive slight fluctuations in cerebral microcirculation are tolerated by the brain due to its CBF autoregulation capacity [22]. However, beyond certain thresholds, these fluctuations, most often translated by a chronic reduction in cerebral microcirculation, trigger the formation of a slightly hypoxic microenvironment at the NVU, which is though to be the first initial step involved in initiating NVU injury [23] (Figure 1). At this stage, NVU injury triggers BBB's loss of function and neurovascular uncoupling [23], thus marking the first pathological steps involved in triggering the neurodegenerative cascades and progressively leading to neurodegeneration. This "outside-in" hypothesis suggests that a sufficiently impaired cerebral microcirculation (i.e. outside) in causatively involved in NVU dysfunction and neurodegenerative

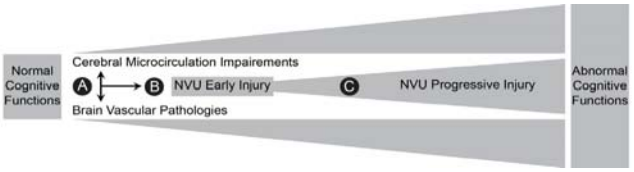

Figure 1: NVU injury initiation, progression and dementia development. A schematic illustration that outlines the pathological links between NVU injury and dementia development, which is based on the existing reports and hypotheses.
(A) The neurodegenerative cascades are triggered as early as the pathological interaction between cerebral microcirculation impairments and brain vascular pathologies occurs**.**
(B) In turn, cerebral microcirculation impairments associated to, or caused by, brain vascular pathologies, initiate the early events involved in NVU injury.
(C) The early injury of the NVU initiates the first steps involved in triggering the neurodegenerative cascades. Over time, this injury evolves to a progressive one and gets exacerbated by chronic cerebral microcirculation impairments associated to brain vascular pathologies, thus aggravating the neurodegenerative cascades and leading to dementia.

cascades initiation (i.e. in). In addition, the novel two-hit vascular hypothesis for neurodegeneration has integrated an additional "inside-out" aspect involved in NVU dysfunction. This aspect is marked by BBB's loss of function that is mainly caused by pericyte detachment and death [3]. This hypothesis suggests that pericyte loss, due to multiple intrinsic (e.g. age) and/ or extrinsic (vascular pathologies) factors, induces BBB breakdown and consequently the entry of blood-borne proteins into the brain, namely albumin, thus triggering cerebral edema formation [3]. The local increased pressure that is caused by cerebral edema directly causes regional tissue hypoperfusion, thus contributing to the formation of a hypoxic microenvironment at the NVU, which initiates the neurodegenerative cascades and neuronal dysfunction [3] (Figure 1). In turn, neuronal dysfunction aggravates the vascular damage by negatively affecting neurovascular coupling, which leads to a progressive reduction in CBF, NVU injury exacerbation and consequently neurodegeneration. Beside its role in maintaining a functional BBB, the NVU deeply shapes brain innate immune system [24]. Historically, the brain was thought to be immune deprived due to the presence of the BBB. However, following extensive investigations, it has been shown that the brain possesses a specialized intrinsic innate immune system [24]. Microglia constitute the powerhouse of the innate immune system in the brain [24]. Microglia rapidly respond to the immune cues present in their microenvironment, which is controlled by the NVU [25]. For instance, BBB breakdown following NVU injury allows the entry the blood-borne molecules into the brain, which can trigger microglial cell activation, namely fibrinogen that has been shown to activate microglia by binding microglial Cluster of Differentiation 11b (CD11b) and Toll-Like Receptors (TLRs) [25]. The activation of microglia induces the production of free radicals and proteases that potentiate NVU injury exacerbation [25]. In parallel to this process, the formation of a hypoxic microenvironment at the NVU directly contributes to the inflammatory process by regulating several genes involved in inflammation [26]. For example, Hypoxia-Inducible Factor 1α (HIF1α) constitutes an early inducer of genes involved in the inflammatory responses at the NVU, namely the inflammatory cytokine interleukin 1β (IL1β) [26]. This early step is followed by the propagation of the inflammatory responses due to the continuous production of inflammatory cytokines, such as interleukin 1β, and the subsequent pathological activation of microglia by this cytokine [27]. Taken together, these observations highlight the implication of cerebral microcirculation impairments associated to, and/ or caused by, NVU injury, as a crucial step involved in initiating the neurodegenerative cascades observed in AD and VaD. Over time, the progressive reduction in CBF accentuates, a phenomenon that exacerbates the early neurodegenerative cascades that were already triggered, which will result in brain atrophy and cognitive decline [15] (Figure 1).

NVU repair: A promising therapeutic avenue

Despite all efforts, no efficacious treatment exists for treating and/ or preventing dementia-related disorders, such as AD and VaD. The recent technical and scientific advances underlined the major contribution of NVU injury in the development of the neurodegenerative cascades, which specifically provided a new integrative approach that will allow the scientific community to get better insights into the pathogenesis of AD and VaD. Such a holistic approach would help in the development of novel therapeutic strategies based on NVU protection and/ or repair. It is noteworthy to mention that the NVU constitutes an interesting therapeutic target on its own, due to its relative accessibility for numerous systemic and minimally invasive therapeutic interventions. Targeting the NVU in dementia-related disorders is still an emerging field and a lot remains to be achieved. However, lessons from cerebrovascular disorders, such as ischemic stroke, clearly demonstrated the potential of such a strategy in rescuing neuronal function. For example, the systemic delivery of the Liver X Receptor (LXR) agonist triggered NVU repair following ischemic stroke, mainly by reducing brain edema, enhancing BBB physical integrity, increasing ABCB1 expression and reducing the activity of proteases involved in ECM protein degradation [28]. Indeed, the administration of a LXR agonist decreased the pro-inflammatory responses of microglia and enhanced their phagocytic capacity, which resulted in the deceleration of AD pathogenic features [29]. Interestingly, other nuclear receptors, such as peroxisome proliferator-activated receptor γ (PPARγ), have been demonstrated to be very promising in treating dementia-related disorders [30]. For instance, PPARγ activation has been reported to enhance microglial cell phagocytic capacity towards Aβ, without triggering pro-inflammatory responses, thus reducing cerebral and vascular Aβ [31]. The cellular composition of the NVU makes it also an interesting target site for several cell therapy approaches. For example, the systemic administration of neural precursor cells (NPCs) induced NVU repair by stabilizing the BBB and reduced the generation of free radicals following ischemic stroke [32]. Interestingly, the transplantation of Mesenchymal Stem Cells (MSCs) reduced the production of pro-inflammatory cytokines by activated microglia at the NVU and consequently enhanced cerebral Aβ clearance [33]. Moreover, targeting the pericytes at the NVU seems also to be a very promising approach to promote NVU repair [34,35]. For example, Vitamine D has been reported to mediate profound protective effects in neurodegenerative disorders, mainly by rescuing pericytes at the NVU [36]. However, a big gap exists in the literature, and it is now urgent to further investigate these new avenues in clinically relevant animal models of dementia-related disorders. Finally, it is important to recall that AD and VaD are heterogeneous multifactorial diseases, which render the development

of efficacious treatments even more challenging. Meanwhile, simple strategies that aim to maintain NVU function by minimally reducing the major risk factors that are implicated in vascular dysfunction and cerebral microcirculation impairments, such as diet, smoking, etc. should be adopted to prevent, or at least delay, the initiation and the propagation of the neurodegenerative cascades observed in AD and VaD [4].

Conflict of Interest Statement

The author declares that the present work was conducted in the absence of any potential conflict of interest.

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