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Cell-to-Cell Communication and Vascular Dementia

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Abstract

Vascular Dementia (VaD) is the second most common form of dementia second only to that caused by Alzheimer's Disease. As the name indicates, VaD is predominantly considered a disease caused by vascular phenomena. In this opinion, we introduce the reader to recent developments in defining VaD as a unique form of dementia. We discuss the clinical and experimental evidence which supports the notion that the microcirculation, specifically cell-to-cell communication, likely contributes to the development of VaD. Through exploration of the concept of the neurovascular unit, we will elucidate the extensive cerebro-vascular communication which exists and highlight models which may help test the contribution(s) of cell-to-cell communication at the microvascular level to the development and progression of VaD. Lastly we explore the possibility that some dementia, generally considered to be purely neurodegenerative, may actually have a vascular component at the neurovascular level. This recognition potentially broadens the critical involvement of microvascular events that contribute to the numerous dementias affecting an increasingly larger sector of the adult population.

Keywords

Dementia; neurovascular unit; cerebral microcirculation; animal model; cell-to-cell communication; tauopathy; CADASIL

Introduction

Can failure of cell-to-cell communication on the microvascular level contribute to dementia? Since the discovery that nitric oxide released from endothelial cells directly regulates smooth muscle tone [18, 28], direct cell-to-cell communication between vascular cells has become an integral part of our understanding of vascular regulation. It is therefore not surprising that pathologies such hypertension or diabetes include a failure in cell-to-cell communication at the level of the microvasculature [12, 36, 69]. The importance of cell-to-cell communication to overall homeostasis of organ blood supply is exemplified in the cerebral circulation. There is no question that proper brain function requires a continuous, uninterrupted blood supply. Since the brain lacks substantial reserves of nutrients and oxygen, even short interruptions of blood flow result in neuronal dysfunction within seconds and neuronal death when the interruption continues [51]. The seminal work of Roy and Sherrington demonstrated that neuronal activity and local blood flow are well coupled [59]. For this to occur, some form of cell-to-cell communication between the neuronal cells and their activity and the vasculature has to exist. A significant feature of cerebral blood flow regulation is the ability to autoregulate providing for the maintenance of cerebral blood flow

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over a wide range of arterial pressures [55]. While autoregulation is a mechanism primarily attributed to the medium to large size resistance vessels, studies highlighted by Greenberg showed that cerebral blood flow is also regulated at the level of the microcirculation [22]. Thus, both macro- and microcirculations contribute to the regulation of cerebral blood flow. Here we propose to elucidate if a contribution of impaired cell-to-cell communication at the microcirculatory level contributes to the development of dementias in general, and Vascular Dementia (VaD) in particular.

A question of definition

The contribution of vascular factors to the development of dementias has long been suspected. Currently, Alzheimer's Disease (AD) is the predominant pathology responsible for dementia [54]. Alois Alzheimer himself suspected that the disease he described could be linked to some vascular phenomena [2]. The next most common form of dementia is Vascular Dementia [54]. Critical to the task of discerning a connection between cell-to-cell communication and vascular dementia, is to examine the definition of VaD because this should provide insights into the mechanism(s) responsible. Over the years there has been a refinement of what vascular dementia represents. Initially, VaD was considered to be the result of macroscopic strokes as well as repeated mini strokes where the subsequent infarctions result in various degrees of dementia [23]. It became apparent that the existence of various definitions of vascular dementias was hindering comparison of studies and results [21]. The American Heart Association and American Stroke association recognized the need to review vascular contributions to cognitive impairment and dementia and to provide a framework of definitions of dementias to aid researchers and practitioners, and released a Scientific Statement [21]. Based on this, it was determined that numerous forms of dementias may in fact have a vascular origin which have now been classified as a syndrome called vascular cognitive impairment (VCI) with VaD considered the most severe form [21]. The Scientific Statement goes on to define dementia as a decline in at least two cognitive functions independent of any vascular event. They subsequently label it as VaD when both cognitive impairment and imaging evidence of vascular disease is confirmed such as a stroke and onset of dementia or evidence of subcortical cerebrovascular disease such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is an autosomal dominant arteriopathy characterized by a *Notch3* gene mutation that results in smooth muscle degeneration and reduced cerebrovascular function [21, 32, 39]. Based on this, we can conclude that vascular dementia has numerous causes linked to a failure of the macro circulation such as a stroke and/or a failure of the microcirculation as exemplified by mini strokes and CADASIL.

Not All Dementia is Vascular Dementia

It is worth mentioning here that other diseases can cause dementia with or without suspected vascular involvement. There are neurodegenerative dementias which describe the failure of neuronal function independent of any vascular impairment such as frontotemporal dementia (FTD). FTD is a tauopathy caused by a mutation of the micro-tubule associated protein tau (MAPT) gene [11]. Some occurrences of Alzheimer's disease are considered non-vascular disease because no vascular alterations such as the cerebral amyloid angiopathy (CAA) or other vessel lesions could be detected [29]. To further complicate the description of VaD, there are combinations of Alzheimer's Disease and VaD called mixed dementia [54]. This heterogeneity complicates the task of understanding the mechanistic basis for dementia.

How does vascular cell-to-cell communication cause or contribute to VaD?

The most common contributor to vascular dementia appears to be a stroke and the subsequent infarction [23]. As such, macroscopic stroke involves the temporary or

permanent occlusion of larger arterial vessels. If the occlusion is permanent, then no recovery of the affected tissue can occur. Recanalization and the resultant restoration of blood flow is seen as the most important measure to minimize tissue damage [51]. While recanalization is the first step, the subsequent response of the blood vessel distant to the occlusion and with it the extent of perfusion after recanalization is also important because it is a predictor of tissue recovery [49]. Importantly, although the blood flow in the larger vessels has been restored, one often observes a subsequent cessation of tissue blood flow, the no-reflow phenomenon, which reduces or limits tissue recovery [3, 49]. Several mechanisms for this secondary flow cessation have been postulated including the adherence of lymphocytes plugging the capillaries [3, 57, 61]. In addition, reduced bioavailability of nitric oxide could result in vessel constriction and a diminished endothelial to smooth muscle/pericyte cell communication could partly explain the observed no-reflow phenomenon [16, 47, 73, 78]. Ischemia also can reduce conducted vasomotor responses [42], a mechanism important for the adjustment of proximal blood flow to the local tissue needs [38]. Reduced conducted vasomotor responses to bradykinin after hypoxia and reoxygenation were observed in cerebral arterioles [8, 9], as were enhanced responses to adenosine and adenosine tri-phosphate after ischemia and reperfusion [53]. Conducted responses rely on the initiation of the response and the conduction of an electrical signal via gap junctions [68]. Gap junction communication is reduced after ischemic events [46, 80]. As such a reduction in the initiation of the response as seen with Bradykinin, and/or a reduction of the conduction would manifest itself as a reduced tissue perfusion resulting in neuronal damage and subsequent dementia. Further studies are needed to elucidate if after stroke conducted responses are impaired and how this impairment could lead to neuronal cell death and dementia.

The definition of VaD provides us with two more mechanisms by which vascular events can contribute to VaD, mini strokes and CADASIL. Hachinski first proposed the idea that multiple strokes (large and small) contribute to dementia and coined the term multi-infarct dementia (MID) [23]. Mini strokes, which are strokes in the small cerebral vessels, are clearly in the domain of the microcirculation. In the clinic, such strokes are often silent and not detected as such [71]. However, recent imaging studies revealed that silent strokes may significantly worsen cognitive ability [70] with a prevalence of such strokes in about 50% of patients who present with a clinical stroke [71]. Such silent strokes may therefore be common in the development of VaD. It is also not clear how cell to cell communication contributes to a vascular impairment leading to dementia. However, it is reasonable to conclude that mechanisms similar to those responsible for cell-to-cell communication failure in larger vessels apply to microvessels, maybe even more so because of the close vicinity of microvessels and neurons.

Of the definitions offered for VaD, CADASIL provides a clearer connection between a disease process involving the microcirculation and dementia. Imaging studies demonstrate extensive white matter lesions, lacunar infarcts, microbleeds, and brain atrophy [72]. In an animal model of CADASIL, this arteriopathy manifests itself in reduced vasodilatory responses with increased sensitivity to phenylephrine-induced pressor responses but without the development of the vasculopathy which also affects the morphology of pericytes and endothelium of cerebral capillaries [65]. This could indicate that besides the CADASIL induced rarification of arterioles and capillaries which reduces blood flow, cell-to-cell communication is also impaired thus possibly contributing to dementia. While the vascular disturbances precede parenchymal lesions [31, 39], it has yet to be determined if dementia-like symptoms occur at this stage or how microvascular cell-to-cell communication contributes to the CADASIL-induced dementia. Animal models for CADASIL exist [60] but so far there have been no studies using this model to examine cognitive function loss related to the disease. If a relationship between cognitive function loss and the development could

be established, then we could design experiments to interfere with the development of CADASIL by attempting to reduce the observed vessel rarification possibly through growth factor stimulation [79].

Is cell-to-cell communication involved in the development of VaD? A look at the neurovascular unit

Proper blood flow regulation of the brain involves both the macrocirculation and microcirculation. The macrocirculation provides the pressure to supply the brain with blood. The microcirculation, however, is responsible for matching local cerebral blood flow to neuronal activity. Understanding of how local cerebral blood flow is matched to neuronal activation requires an understanding of the role of the neurovascular unit (NVU). The concept of the neurovascular unit was introduced by the Stroke Progress Review Group who defined the NVU as the triad of neurons, glia (such as astrocytes and microglia) and adjacent microvessels (arterioles and capillaries) [67]. In the NVU, neuronal activity is signaled to the surrounding glia, which in turn signals to the adjacent microvessels to cause an increase in cerebral blood flow. Thus cell-to-cell communication occurs from neuron to glia to microvascular cells (smooth muscle, pericyte and endothelium). Failure of proper neural activity communication at each step could result in failure of the microcirculation to adjust local blood flow resulting in neuronal damage or death. There is ample evidence that neuronal activation results in increased cerebral blood flow. However, demonstration of the mechanisms involved and the contribution of the cells comprising the NVU is still far from complete.

In addition, metabolic factors such as reduced oxygen tension or increased adenosine concentrations due to neuronal activity may influence neurovascular unit function. In erythrocyte perfused cerebral arterioles Dietrich et al. showed *ex vivo* that reducing extravascular oxygen tension released adenosine 5' tri-phosphate from the erythrocytes causing arteriolar vasodilation [7]. Reduced oxygen tension also caused astrocytic release of adenosine 5'tri-phosphate with a subsequent increase in adenosine concentration [37] which correlated with adenosine increases observed *in vivo* [75]. While neuronal activity and the release of neurotransmitters can be considered to be the initial stimulus to adjust local blood flow through neurovascular unit activity it is likely that metabolic signaling molecules such as oxygen tension also contribute to local blood flow regulation similar to observations in skeletal muscle [50].

Recently, significant evidence in support of a central role of astrocytes in neurovascular coupling was obtained in experiments performed mainly in brain slice preparations. Activation of astrocytes during synaptic transmission leads to elevation of astrocytic calcium (Ca^{2+}), which in turn activates enzymes within both astrocytes and cerebral vessel cells to generate vasoactive substances [20, 27]. Astrocytes can release vasoactive agents; and may also transfer Ca^{2+} elevations to vascular endothelial cells which, in turn, may release vasodilating agents [13]. However, the precise cellular source of these vasoactive agents which regulate cerebral microcirculation have not yet been determined [27]. Potential agents released after astrocyte activation induce cerebral vasodilation [66, 81], but also vasoconstriction [52]. Several vasoactive mediators have been implicated in the vascular responses, including the dilators Prostaglandine E_2 [66, 81], epoxyeicosatrienoic acids (EETs) [4, 43, 45, 48], adenosine tri-phosphate ATP [26, 56, 63, 77], potassium ion (K^+) [15], and carbon monoxide (CO) [41] and the constrictor 20-hydroxyeicosatetraenoic acid (20-HETE) [19, 43, 48, 52]. The seemingly diverse observations in these previous studies may be the result of the complexity of cellular components in the neurovascular unit which may make it difficult to identify the precise signaling molecules and their cellular sources or may reflect different regulatory mechanisms depending on the species studied. To date, no

study has directly linked failure of astrocyte function with the development of dementia. However, studies have indicated that astrocytic dystrophy as well as astrogliosis may contribute to various dementias. Two studies examined astrocyte content in frontotemporal dementia and both concluded that changes in astrocyte content is the earliest anatomical indicator in the development of the dementia [6, 33]. Interestingly, Broe et al. found astrocytic dystrophy while Kersaitis et al. demonstrated gliosis to be present in early frontotemporal dementia. A possible explanation for this difference may be in the methods used. Where Broe et al measure apoptotic astrocytes, Kersaitis et al. utilize an antibody stain which does not indicate dead astrocytes. In either case, it is not known how an altered astrocyte content, either dystrophic or gliotic, may influence neurovascular unit function. Altered astrocyte content was also reported in a model of CADASIL where Brennan-Krohn et al. measured molecular blood vessel and astrocyte markers [5]. They conclude that CADASIL is mediated by both glial and vascular degeneration and may contribute to impaired function of vascular and glial cytoskeletons [5]. However, how such glial or vascular degeneration adds to the development of CADASIL was not studied. Further, the study did not suggest how glial degeneration could affect neurovascular function in the context of CADASIL and thus needs further research.

Are there experimental models to study VaD?

A challenge to test if cell-to-cell communication contributes to dementia is a lack of appropriate animal models. Though animal model for CADASIL exist [60] this model has not been used to test for loss of cognitive function. Such function loss has been studied in other dementia inducing diseases such as Alzheimer's [35]. As such it should be possible to apply such methods to other models of VaD. Another challenge is the complexity of the NVU which makes it difficult to establish the contribution of each NVU cell type and the molecular mechanism involved and to then test if impairment of cell-to-cell communication contributes to VaD. In the past, human studies have utilized brain slice preparations to evaluate communication between astrocytes and microvessels [14, 15, 63]. However the results obtained by such studies are often conflicting [20, 25] though eliminating a special astrocyte layer, the glia limitans, did decrease vascular reactivity *in vivo* [76]. It may therefore be necessary to initially go to an even more reductionist approach to resolve the molecular pathways of neurovascular cell-to-cell communication. One approach would be to study *ex vivo* the effect of neurotransmitter stimulation of astrocytes on the vessel diameter of isolated arterioles [10]. In this model it is possible to precisely study the effects of a neurotransmitter (as a neuronal surrogate) on vascular response with or without the presence of astrocytes (glia). With the knowledge of the molecular pathways involved, one could progress to specific transgenic animal models to test if a cell-specific alterations of the molecular pathway causes dementia in the model as tested by cognitive evaluation. There are now cell-type specific knock-out animals such a pericyte deficient knockout mouse [74] that would allow one to determine the contribution of such cells to cerebro-vascular regulation and cell-to-cell communication of the NVU.

Risk factors, VaD and NVU

So far we discussed VaD as a singular disease. However, in many disease processes additional independent risk factors may contribute to the development or severity of the disease. Numerous risk factors have been identified that can enhance the likelihood of developing VaD including unmodifiable factors such the apolipoprotein $\epsilon 4$ allele but also high blood pressure or glucose and smoking [58, 71]. Jones et al. found a significant correlation between the apolipoprotein $\epsilon 4$ allele and VaD [30]. In their review Altman and Rutledge strongly suggest that the apolipoprotein $\epsilon 4$ allele contributes to the development of Alzheimer's Disease possibly via lipid toxicity damaging the cells of the neurovascular unit

[1]. However, it is not known if lipid toxicity directly contributes to the development of VaD.

Neurodegenerative disease: Can neurological dysfunction lead to failure of NVU regulation and local blood flow and enhance neuronal damage or death?

So far we have looked at the paradigm that neuronal activation leads to increased blood flow and that a failure of the subsequent signaling system of glia and/or microvessels leads to a disturbed blood supply and thus neuronal damage or death resulting in dementia. But what if the neuron fails to send the appropriate signal? Then the microcirculation would not receive a signal to adjust blood flow to accommodate the local tissue needs. Neuronal degenerative disease is presumed to be independent of vascular contributions but is it?

The question arises if neurodegenerative dementia is a form of microvascular VaD?

To elucidate the question above we have to look at angioneurins, essentially growth factors such as vascular endothelial growth factor (VEGF) which allows for a communication between neurons and the microvascular cells [79]. As an example, VEGF is produced by cells experiencing hypoxia including endothelial cells [34, 44, 62] and neurons [24]. Basal VEGF is needed to maintain microvascular function and integrity [40]. Neuronal activity also enhances angiogenesis, indicating a close link between neuronal activity and the plasticity of the microvasculature. Conversely, lack of neuronal activity or an inability of the neuron to release/induce angioneurins may result in microcirculatory rarification and as such lead to decreased local blood flow which may lead or enhance neuronal damage or death. If such a communication of angioneurins is needed to allow for proper neurovascular function, then we look at a two way street where not only the microcirculation provides the blood supply to maintain neuronal health, but the neuron itself may need to provide the signals/factors to maintain proper neurovascular unit integrity. Testing if local vascular factors are responsible for neuronal damage or death or if neuronal pathology alone causes dementia is experimentally difficult. However, in recent experiments related to Alzheimer's Disease, Spuch et al. showed that in an animal model of Alzheimer's Disease implantation of encapsulated VEGF producing cells decreased amyloid and Tau burden and improved cognitive function [64]. Similar experiments could be applied to animal models replicating neurodegenerative dementias such as frontotemporal dementia (FTD). FTD is a degenerative disease primarily caused by mutations of MAPT [11]. Animal models of tauopathies and the related FTD exists [17]. It would be of significant interest to determine if cognitive function is restored in such a model when an angioneurin signaling system is present.

Perspective

This brief survey shows that there are numerous pathologies that can result in dementia and within these pathologies are several that include vascular phenomena. When concentrating on the purest syndrome of vascular dementia (VaD) there is ample evidence that vascular events contribute to the development of dementia. While the current survey seems to indicate that impaired cell-to-cell communication at the neurovascular level may contribute to the development of dementia, more clinical and experimental data are needed to confirm or refute this hypothesis. Further, there is a possibility that some dementias previously considered purely neurodegenerative may have a neurovascular component thus extending the contribution of neurovascular cell-to-cell communication in the disease process of dementias.

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List of Abbreviations

VaD	vascular dementia
AD	Alzheimer's Disease
VCI	vascular cognitive impairment
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
FTD	frontotemporal dementia
CAA	cerebral amyloid angiopathy
MAPT	micro-tubule associated protein tau
MID	multi-infract dementia
NVU	neurovascular unit
VGEF	vascular endothelial growth factor

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