Cerebral microvascular dysfunction and neurodegeneration in dementia

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ABSTRACT

Maintaining normal learning and memory functions requires a high degree of coordination between neural and vascular cells. Basic and clinical studies have shown that brain microvasculature dysfunction activates inflammatory cells in the brain, leading to progressive neuronal loss and eventually dementia. This review focuses on recent studies aimed at identifying the molecular events that link cerebral microvascular dysfunction to neurodegeneration, including oxidative/nitrosative stress, cellular metabolic dysfunction, inflammatory signalling and abnormal synaptic plasticity. A better understanding of the coupling between vasculature and brain neurons and how this coupling is disrupted under pathological conditions is of great significance in identifying new diagnostic and treatment targets for dementia for which no new drugs have been approved since 2003.

Accumulating evidence from epidemiological and postmortem studies suggests a close relationship among small vessel disease (SVD), aberrant neurovascular regulation and cognitive impairment. Dysregulation of cerebral blood flow and abnormal neural activity secondary to altered neurovascular coupling have been observed in the early stage of neurodegenerative diseases. However, the precise mechanism by which vascular dysfunction contributes to cognitive impairment remains poorly understood.

Aberrant peroxynitrite generation is a primary risk factor for vascular dysfunction. Patients with Alzheimer’s disease (AD) exhibit clear cerebrovascular pathology and white matter injury due to microvascular infarction, suggesting an association of the cerebrovascular disease with neurodegenerative disorders. A possible contribution of nitrosative stress to AD pathology is indicated by the observation that peroxynitrite formation induced microvascular injury followed by β-amyloid accumulation in microvessels and parenchyma and eventual Glycogen synthase kinase-3β (GSK3β) activation and hyperphosphorylation of tau proteins in the aged rat brain. Supporting this suggestion, inhibition of nitrosative stress partially restored the decrease of phospho-CaMKII (Thr286/287) and phospho-synapsin I (Ser603) and phospho-GluR1 (Ser831) are dramatically decreased in the diabetic mice with ischaemia. Together, these findings suggest an active role for vascular factors in the pathogenesis of cognitive dysfunction. Further studies are needed to fully understand the changes in the microenvironment in the brain under the different pathological condition and the communication between components of the neurovascular unit.

Emerging studies have uncovered essential roles of endothelial molecules in brain function and behaviour. For example, brain endothelial cells have been suggested to be a natural gatekeeper for virus-induced sickness behaviour. The study further demonstrated an engagement of tissue-specific Interferon (IFN) receptor chain 1 and established the signal transduction axis as a target for the treatment of the behavioural changes. Clinical studies suggest that endothelial thrombomodulin is closely associated with cerebral SVD severity, but cerebral endothelial activation in

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Figure 1 The schematic image is illustrating the possible relationship between cerebral microvascular dysfunction and neurodegeneration in dementia.

...deep penetrating arteries did not. By using both endothelial-specific gene knockdown and neurobehavioural strategies, we found that deletion of the endothelial ErbB4 receptor-induced impairment in exploratory activity in adult mice and the effect was associated with reduced glucose transport and impaired energy metabolism of the brain. More recently, the study showed that brain endothelial-derived semaphorin 3G might act as a synaptic organiser, regulating synaptic plasticity and hippocampal-dependent memory.

A long list of endeavours are warranted to further tackle the mechanisms underlying the interaction between vascular and neuronal cells and the role of the interaction in dementia, including (1) studies using novel technologies including imaging from nanoscale to whole brain, high-throughput transcriptomics/proteomics screens and bioinformatics, (2) a deeper understanding of the dynamic regulation of neurovascular coupling by circulatory factors including those implicated in dementia, and (3) further exploration of the role of exosomes, cytokines and microRNAs in microvascular compartments. A combination of these approaches may allow for multidimensional analyses of the complex underlying molecular and cellular network, help discover novel biomarkers, and develop more effective diagnostic and treatment strategies for dementia.

