The Role of Perlecan Domain V in Vascular Dementia

https://www.neurodegenerationresearch.eu/survey/the-role-of-perlecan-domain-v-in-vascular-dementia/

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USA

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The Role of Perlecan Domain V in Vascular Dementia

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NIH (NIA)

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The project/programme is most relevant to:

Alzheimer's disease and other dementias

Keywords

perlecan, Vascular Dementia, Carotid Stenosis, Bilateral, cerebrovascular

Research Abstract

DESCRIPTION (provided by applicant): Despite its prevalence, VaD remains woefully understudied and poorly understood, in part due to its diverse etiology. The outcome of these multiple causes of VaD, however, remains the same- disruption of the complex coupling

between endothelial cells, astrocytes, pericytes, neurons, and the extracellular matrix, the components of the neurovascular unit. We hypothesize that the extracellular matrix plays a critical role in the neurovascular disruption of VaD. In particular, we have identified a biologicaly active fragment of one prominent matrix component, the heparan sulfate proteoglycan, perlecan, to play a major role in regulating endothelial cell function after experimental ischemic stroke. This fragment, termed domain V (DV), is actively generated in the stroked brain and appears to be important to the brain’s response to injury inasmuch as its absence results in more significant stroke injury and worse outcome. Furthermore, DV stroke treatment after stroke enhances peri-infarct new blood growth (angiogenesis) and important component of neurorepair. As extracellular matrix remodeling is likely to occur in the vascular pathology leading to VaD, we hypothesize that DV is actively generated, plays a key role in regulating brain endothelial cell function, and may improve endothelial cell function and neurovascular coupling when administered in two experimental mouse models of VaD, the BCAS and the DB/AD models, which differentially impact white matter and gray matter, respectively. This will allow us to determine both the impact of white and gray matter endothelial cell dysfunction on VaD and DV’s potential impact on it. To investigate these hypotheses, we propose three aims: Aim 1. Determine the extent and significance of DV generation in the BCAS and DB/AD mouse models. Aim 2. Determine the therapeutic potential of DV in the BCAS and DB/AD mouse models. Aim 3. Determine the extent and significance of DV generation in human autopsy brain from subjects with VaD. Successful completion of these studies will increase our understanding of the role of the extracellular matrix and angiogenesis in VaD, and support the therapeutic potential for DV.

Lay Summary
PUBLIC HEALTH RELEVANCE: Although vascular dementia is the second leading cause of dementia behind Alzheimer’s disease, it remains woefully understudied and poorly understood, in part due to its diverse etiology. The gradual failure of compensatory new brain blood vessel formation (angiogenesis) in the face of ongoing cerebrovascular insult appears to contribute to vascular dementia, regardless of the etiology. We propose to determine the role and therapeutic potential of an angiogenic extracellular matrix fragment in human and novel animal models of vascular dementia.

Further information available at:

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