Endothelial eNOS-deficient mice as chronic cerebral hypoperfusion model

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Research Abstract

? DESCRIPTION (provided by applicant): Vascular risk factors such as high cholesterol, ApoE genotype, and diabetes play a critical role in the development of cognitive decline during aging and disease, such as vascular dementia and sporadic Alzheimer’s disease (SAD). These risk factors often result in chronic cerebral hypoperfusion and microvascular pathology. Together with cerebral amyloid angiopathy (CAA), they represent core pathophysiological features of AD.

Cerebral hypoperfusion/ hypometabolism is a pre-clinical event in AD, which most accurately predicts the probability of a patient to develop AD. Our preliminary data demonstrate that, when compared to eNOS+/+ littermates, eNOS-deficient mice (+/-,16-18 MO) display marked CAA, microbleeds, BBB disruption, and severely impaired spatial working memory. Moreover, multiple localized vessel occlusion, as detected by FITC-dextran angiography, was found in three selected areas (temporoparietal cortex, hippocampi and cingulate), matching precisely the hypoperfused areas identified in early AD patients. Based on our findings, we hypothesize that chronic cerebral hypoperfusion and aberrant generation of amyloid are the two key components forming the vicious cycles for vascular dysfunction and dementia. Herein, we propose to implement a combination of state of the art methodologies, such as cranial window and two-photon imaging techniques in living mouse brains to further study cerebrovascular dysfunction in eNOS-deficient mice. Aim 1. Determine eNOS-driven pathophysiological mechanisms underlying microvascular occlusion. We will utilize combined use of immunohistochemistry/FITC-dextran angiography and EM to identify the involved cell types and abnormalities in the areas of CAA/hypoperfusion and occlusion in eNOS deficient vs. control mice. Molecular changes in affected areas will be detected by qRT-PCR on the isolated individual loci using Laser-capture microdissection (LCM). Using intravital microscopy in a cranial window, we will determine the interval at which hypoperfusion occurs in eNOS mice, and whether this pathophysiological event is a) transient or rather permanent, and b) reversible upon eNOS functional restoration. Aim 2. Determine that intravascularly deposited A? and CAA play a pathophysiological role in the vascular abnormalities and occlusion found in partial eNOS deficient mouse. To test this aim, we will sequentially address a series of questions: 1) When and where does CAA occur? 2) Does the chronic hypoperfusion condition in young adult eNOS mice promote local A? generation, increased uptake of A? from peripheral plasma, or both? 3) Does CAA vessel display structural and functional abnormalities? Confirmation of a pathophysiological role for A? will be determined by demonstrating that the abnormalities found in 1) to 3) are reversed/ameliorated by A? suppressing therapies, either systemically (gelsolin or ganglioside/GM1) or locally (?-secretase inhibitor).

Further information available at:

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