Brain microvascular injury and white matter disease provoked by diabetes-associated hyperamylinemia

Han Ly [1] • Nirmal Verma, PhD [1] • Fengen Wu [1] • Miao Liu, PhD [1] • Kathryn Saatman, PhD [2] • Peter Nelson, MD, PhD [3] • John Slevin, MD [4] • Larry Goldstein, MD [5] • Geert Jan Biessels, MD, PhD [6] • Florin Despa, PhD [1]

[1]Pharmacology and Nutritional Sciences, University of Kentucky • [2]Physiology, Spinal Cord and Brain Injury Research Center, University of Kentucky • [3]Sanders-Brown Center on Aging, University of Kentucky • [4]Neurology, Veterans Administration Medical Center, University of Kentucky • [5]Neurology, University of Kentucky • [6]Neurology, University Medical Center Utrecht

Objective:
The brain blood vessels of patients with type 2 diabetes and dementia have deposition of amylin, an amyloidogenic hormone cosecreted with insulin. It is not known whether vascular amylin deposition is a consequence or a trigger of vascular injury. We tested the hypothesis that the vascular amylin deposits cause endothelial dysfunction and microvascular injury and are modulated by amylin transport in the brain via plasma apolipoproteins.

Methods:
Rats overexpressing amyloidogenic (human) amylin in the pancreas (HIP rats) and amylin knockout (AKO) rats intravenously infused with aggregated amylin were used for in vivo phenotyping. We also carried out biochemical analyses of human brain tissues and studied the effects of the aggregated amylin on endothelial cells ex vivo.

Results:
Amylin deposition in brain blood vessels is associated with vessel wall disruption and abnormal surrounding neuropil in patients with type 2 diabetes and dementia, in HIP rats, and in AKO rats infused with aggregated amylin. HIP rats have brain microhemorrhages, white matter injury, and neurologic deficits. Vascular amylin deposition provokes loss of endothelial cell coverage and tight junctions. Intravenous infusion in AKO rats of human amylin, or combined human amylin and apolipoprotein E4, showed that amylin binds to plasma apolipoproteins. The intravenous infusion of apolipoprotein E4 exacerbated the brain accumulation of aggregated amylin and vascular pathology in HIP rats.

Interpretation:
These data identify vascular amylin deposition as a trigger of brain endothelial dysfunction that is modulated by plasma apolipoproteins and represents a potential therapeutic target in diabetes-associated dementia and stroke.