Gait Abnormalities, Impaired Balance and Brain White Matter Hyperintensities in a Rat Model of Late-Onset Type-2 Diabetes

Han Ly[1] • Nirmal Verma, PhD[1] • Fengen wu[2] • Aurel Popa-Wagner, PhD[3] • Florin Despa, PhD[1]

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[1]Pharmacology and Nutritional Sciences, University of Kentucky • [2]College of Art and Science, University of Kentucky • [3]Psychiatry, Rock stock University Medical School

Introduction: Diffuse brain white matter disease is highly prevalent in type-2 diabetes and has been clinically associated with vascular contributions to cognitive impairment and dementia in humans. However, the underlying mechanisms are not clearly understood. Recent data, including our work, suggest that mechanisms of diabetic brain injury in humans involve the cerebrovascular accumulation of aggregated amylin, an amyloidogenic hormone synthesized and co-secreted with insulin by pancreatic β-cells.

Hypothesis: Circulating aggregated amylin accumulates in brain blood vessel walls and microvessels leading to chronic ischemia and white matter lesions.

Methods: Because amylin from rodents neither forms amyloid nor accumulates in cells and tissues when being hypersecreted, we used rats expressing human amylin in the pancreas (HIP rats; n=10) rats to mechanistically decipher pathophysiological processes associated vascular accumulation of aggregated amylin. Wild-type littermate male rats (WT group; n=10) served as controls. To identify initial tissue targets of amylin deposition, we generated amylin knockout (Amy-KO) rats (n=3) which were injected with aggregated human amylin (2 µg/g b.w., i.v., q.d.) for 5 days followed by euthanasia and tissue collection. Amylin deposition was tested with an amylin antibody (E-5, Santa Cruz).

Results: HIP rat males develop type-2 diabetes (non-fasted blood glucose >200mg/dl) at 12 mo. of age which correlates with the impairment of exploratory drive and performance on the rotarod test. At 15 mo. of age, HIP rats show gait abnormalities, impaired balance, and white matter hyperintensities on T2-weighted MRI scans (leukoaraiosis). Multifocal infarction in the periventricular region, small subcortical infarcts, and white matter rarefaction were detected in HIP rat brains. These pathologic changes are associated with vascular amylin deposition involving small arteries and capillaries. Amy-KO rats intravenously injected with aggregated human amylin showed amylin deposition in the choroid plexus and capillaries in the periventricular region. Circulating aggregated amylin appears to interact with endothelial cells that became swollen and blocked the lumen of the capillary.

Conclusion: Circulating aggregated amylin contributes to the development of small vessel disease and leukoaraiosis in type-2 diabetes.