## Diabetes and the Brain: A hidden trigger of brain white matter disease

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Type-2 diabetes increases the risk of cerebrovascular disease, but the mechanisms remain incompletely understood. We (and others) recently found that brain blood vessels of patients with type-2 diabetes, particularly those with vascular disease, contain large deposits of amylin, an amyloidogenic hormone synthesized and co-secreted with insulin from pancreatic islets.

Intriguingly, our feasibility study showed a >4-fold higher amylin level in brains of APOE4 carriers with type-2 diabetes compared to non-diabetics, suggesting a link of amylin pathology with type -2 diabetes and APOE genotype. Of note, the amyloidogenicity of amylin is specific to humans (but, not rodents). Using rats that express human amylin in the pancreas ("HIP" rats) and amylin knockout (Amy-KO) rats, we found that amylin deposition in brain blood vessels i) is promoted by circulating oligomerized amylin, ii) involves the interaction with low density lipoproteins (LDL), iii) negatively affects gait, vestibulomotor function and exploratory drive, and iv) develops later in females compared to males (by ~6-9 months). HIP rat brains present deep intracerebral hemorrhages (ICH), capillary loss, white matter rarefaction (leukoaraiosis), and reduced neural protein synthesis (particularly, catecholamines). Based on these preliminary findings, we propose the hypothesis that circulating oligomerized amylin is a pathologic substrate for vasculopathy. In my presentation, I will focus on our plan to use both human biospecimens and novel translational animal models to further understand the impact of amylin deposition on the cerebrovasculature.