Amylin vasculopathy, a novel mechanism of cerebrovascular injury and neurologic deficits in diabetes

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Human amylin is an amyloidogenic hormone that forms toxic oligomers that kill the insulin- producing β-cells in the pancreas of patients with type-2 diabetes. We recently showed that the pancreatic amylin pathology is also linked with cerebrovascular dementia and diabetic heart disease by increased circulating levels of toxic oligomerized amylin. Here, we tested the hypothesis that the cerebrovascular accumulation of oligomerized amylin injures the brain, leading to neurologic deficits independently of hyperglycemia.

A diabetic rat model overexpressing amyloidogenic human amylin in the pancreas (the HIP rat) and appropriate controls were used to investigate mechanistically cerebrovascular effects of amylin accumulation. As controls, we employed wild-type (WT) littermates and age- and glucose-matched diabetic rats expressing only non-amyloidogenic WT amylin, which does not accumulate in pancreas or other organs. Compared to controls, HIP rats showed reduced exploratory drive, vestibulomotor performance and recognition memory. Cortical arteries isolated from HIP rats displayed a ~40% higher myogenic tone ($P<0.05$), which correlates with an increased mean arterial blood pressure by ~20% ($P<0.05$). We also found elevated lipid peroxidation (by 18±3%; $P<0.05$) and activated Ca2+-mediated hypertrophy signaling in cortical smooth muscle cells from HIP rats compared to control rats. Serial staining with the ED1 antibody and amylin antibody indicates possible activated microglia/macrophages which are clustering in blood vessel areas positive for amylin infiltration. Multiple inflammatory markers are expressed in HIP rat brains compared to control rats, confirming that amylin deposition induces an inflammatory response.

Overall, our data suggest that cerebrovascular amylin deposition is associated with neurologic deficits via mechanisms of vascular dysfunction, oxidative stress and neuroinflammation.