Intraneuronal Amylin Deposition, Peroxidative Membrane Injury and Increased IL-1β Synthesis in Brains of AD Patients with T2D and diabetic HIP rats

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Background: Recent studies, including work from our laboratory, suggest that type-2 diabetes is linked with Alzheimer's disease (AD) by the interaction of amylin (also known as islet amyloid polypeptide) with ß amyloid pathology. Here, we sought to spectroscopically authenticate the presence of amylin in AD brains and identify specific amylin-mediated neurotoxic mechanisms.

Methods: The presence of amylin in brain specimens from AD patients with type-2 diabetes (n=4) was tested by liquid chromatography tandem mass spectrometry (LC-MS/MS). To decipher amylin- mediated neurotoxicity, we investigated tissue specimens from humans, compared human amylin- expressing (HIP) rats (n=15) with age- and glucose-matched diabetic rats expressing only endogenous non-amyloidogenic rat amylin (n=15), studied mice injected with aggregated human amylin versus controls (n=10 per group) and developed in vitro cell models.

Results: LC-MS/MS data convincingly demonstrated that amylin is contained in brain lysates from AD patients. In addition to amylin plaques and mixed amylin-ß amyloid deposits, brains of diabetic patients with AD show amylin immunoreactive deposits inside the neurons. Neuronal amylin formed adducts with 4-hydroxynonenal (4-HNE), a marker of peroxidative membrane injury, and increased (by 45% vs. control; $P<0.001$) synthesis of the proinflammatory cytokine interleukin (IL)-1ß. These pathological changes were mirrored in rats expressing human amylin in pancreatic islets (HIP rats) and mice intravenously injected with aggregated human amylin, but not in hyperglycemic rats secreting wild-type non-amyloidogenic rat amylin. In cultured primary hippocampal rat neurons, aggregated amylin increased IL-1ß synthesis via membrane destabilization and subsequent generation of 4-HNE. These effects were blocked by membrane stabilizers and lipid peroxidation inhibitors.

Conclusions: Elevated blood levels of aggregated amylin can promote brain accumulation of amylin leading to peroxidative membrane injury and aberrant inflammatory responses independent of other confounding factors of diabetes. Present results are consistent with the pathological role of aggregated amylin in the pancreas, demonstrate a novel contributing mechanism to neurodegeneration and suggest a direct, potentially treatable link of type-2 diabetes with AD.