**Aβ efflux impairment and inflammation linked to cerebrovascular accumulation of amyloid-forming amylin secreted from pancreas**

Impairment of vascular pathways of cerebral β-amyloid (Aβ) elimination contributes to Alzheimer disease (AD). Vascular damage is commonly associated with diabetes. Here we show in human tissues and AD-model rats that bloodborne islet amyloid polypeptide (amylin) secreted from the pancreas perturbs cerebral Aβ clearance. Blood amylin concentrations are higher in AD than in cognitively unaffected persons. Amyloid-forming amylin accumulates in circulating monocytes and co-deposits with Aβ within the brain microvasculature, possibly involving inflammation. In rats, pancreatic expression of amyloid-forming human amylin indeed induces cerebrovascular inflammation and amylin-Aβ co-deposits. LRP1-mediated Aβ transport across the blood-brain barrier and Aβ clearance through interstitial fluid drainage along vascular walls are impaired, as indicated by Aβ deposition in perivascular spaces. At the molecular level, cerebrovascular amylin deposits alter immune and hypoxia-related brain gene expression. These converging data from humans and laboratory animals suggest that altering bloodborne amylin could potentially reduce cerebrovascular amylin deposits and Aβ pathology.