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Amylin as a Potential Link between Type 2 Diabetes and Alzheimer Disease

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Martinez-Valbuena et al.¹ provide histological evidence of amylin- β amyloid (A β) and amylin-*tau* cross-seeding in both pancreatic and brain tissues, suggesting a possible connection in the pathogenesis of Alzheimer's disease (AD) and type 2 diabetes. They noted pancreatic amylin-A β and amylin-*tau* deposits in humans with AD in the absence of type-2 diabetes, which the authors interpreted as potential evidence for a role of A β and *tau* tangle pathology in insulin resistance in these subjects. We suggest an alternative interpretation of this finding that we base on four key observations: 1, pancreatic β -cells express and process both the A β protein precursor and *tau* mRNAs² implying that amylin-A β and amylin-*tau* inclusions may originate from the pancreas; 2, affected age-groups and clinical trajectories in type-2 diabetes and late-onset AD generally indicate that diabetes most commonly precedes AD and is associated with an acceleration of the transition from mild cognitive impairment to dementia; 3, consistent with this observation and because rodent amylin is non-amyloidogenic, rodent AD models do not develop type-2 diabetes, whereas pancreatic expression of amyloid-forming human amylin in non-AD rats causes type-2 diabetes, brain amylin deposition and behavior deficits³; and 4, the brain region involved in the central regulation of pancreatic β -cell function (i.e., the hypothalamus)⁴ is affected by AD pathology. Consequently, AD may impair central signaling pathways that regulate amylin secretion leading to pancreatic β -cell dysfunction and impaired clearance of amylin, A β and *tau*. We therefore posit that the presence of mixed amylin-A β or amylin-*tau* inclusions in the pancreatic β -cells of patients with AD may reflect an *in situ* stress response to comorbid endocrine dysfunction and amylin dyshomeostasis.

Martinez-Valbuena et al.¹ highlight the complex mechanisms underlying pancreatic β -cell dysfunction and linked amylin-A β and amylin-*tau* pathology in type-2 diabetes. Taken together with published evidence showing the presence of mixed amylin-A β pathology in human AD⁵, these new data¹ provide support for the hypothesis that overexpression and/or impaired clearance of amyloidogenic proteins (amylin, A β , *tau*) are critical pathological pathways in both type-2 diabetes and AD. Without excluding possible contributions of A β and *tau* tangle pathology to the development of type-2 diabetes, our alternative interpretation only serves to emphasize the need for *in vivo* studies that can further elucidate the temporal sequence of amylin- and A β -mediated pathological events involving type-2 diabetes and AD.

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