Published in final edited form as:

Ann Neurol. 2020 March ; 87(3): 486. doi:10.1002/ana.25668.

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

Florin Despa, PhD[1,2], **Larry B. Goldstein, MD**[2], **Geert Jan Biessels, MD, PhD**[3]

[1]Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY, USA [2]Department of Neurology, University of Kentucky, Lexington, KY, USA [3]Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

Martinez-Valbuena et al.[1] provide histological evidence of amylin-β amyloid (Aβ) 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-Aβ 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 Aβ 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 Aβ protein precursor and *tau* mRNAs[2] implying that amylin-Aβ 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 deficits[3]; 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, Aβ and *tau*. We therefore posit that the presence of mixed amylin-Aβ 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-Aβ and amylin-*tau* pathology in type-2 diabetes. Taken together with published evidence showing the presence of mixed amylin-Aβ pathology in human AD[5], these new data[1] provide support for the hypothesis that overexpression and/or impaired clearance of amyloidogenic proteins (amylin, Aβ, *tau*) are critical pathological pathways in both type-2 diabetes and AD. Without excluding possible contributions of Aβ 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 Aβ-mediated pathological events involving type-2 diabetes and AD.

References

1. Martinez-Valbuena I, Valenti-Azcarate R, Amat-Villegas I et al. Amylin as a potential link between type 2 diabetes and Alzheimer Disease. Ann Neurol 2019;10.1002/ana.25570
2. Miklossy J, Qing H, Radenovic A et al. Beta amyloid and hyperphosphorylated tau deposits in the pancreas in type 2 diabetes. Neurobiol Aging 2010;31:1503–1515. [PubMed: 18950899]
3. Ly H, Verma N, Wu F et al. Brain microvascular injury and white matter disease provoked by diabetes-associated hyperamylinemia. Ann. Neurol 2017;82:208–222. [PubMed: 28696548]
4. Rosario W, Singh I, Wautlet A et al. The brain-to-pancreatic islet neuronal map reveals differential glucose regulation from distinct hypothalamic regions. Diabetes 2016; 65:2711–2723. [PubMed: 27207534]
5. Jackson K, Barisone GA, Diaz E et al. Amylin deposition in the brain: A second amyloid in Alzheimer disease? Ann Neurol. 2013;74:517–26. [PubMed: 23794448]