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Islet Amyloid Polypeptide (IAPP) association with Alzheimer's disease pathology and diagnosis

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Abstract

Amyloid formation is the pathological hallmark of type 2 diabetes (T2D) and Alzheimer's disease (AD). These diseases are marked by extracellular amyloid deposits of islet amyloid polypeptide (IAPP) in the pancreas and amyloid β (Aβ) in the brain. Since it has been shown that IAPP enters the brain and that disparate amyloids can cross-seed each other to augment amyloid formation, we determined if such cross-seeding can occur with the amyloids involved in T2D and AD. We demonstrated that: (1) IAPP promoted oligomerization of Aβ *in vitro* and *in silico*, (2) peripheral injection of IAPP increased murine brain IAPP levels, (3) endogenous IAPP localized to Aβ in plaques in mouse models of AD, (4) IAPP was present in and secreted from astrocytes, and (5) IAPP levels were elevated in AD cerebrospinal fluid (CSF). These observations prompted us to explore a potential mechanism whereby IAPP elevated during metabolic dysfunction enters the brain to cross-seed Aβ and augment AD pathology. We tested this mechanism in both humans and transgenic mice, correlating peripheral levels of IAPP with AD pathology. In African Americans, a group with increased risk for both T2D and AD, peripheral IAPP levels were not significantly different in samples with no disease, T2D, AD, or both T2D and AD. Furthermore, in the Tg2576 AD mouse model, IAPP plasma levels were not significantly elevated at an age where the mice exhibit the glucose intolerance of pre-diabetes. Based on this data, it appears unlikely that peripheral IAPP cross-seeds Aβ pathology in AD brain. However, we provide evidence for a novel association between brain derived IAPP and AD, which suggests that brain derived IAPP plays a role in Aβ oligomerization and AD pathology. This potential connection, along with IAPP's known role in weight and memory loss, requires further research.

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