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# PsychoAAD-2013: Islet amyloid polypeptide (IAPP) association with Alzheimer's disease pathology and diagnosis

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Amyloid formation is that 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) within the pancreas and amyloid β (Aβ) within the brain. Since it's been shown that IAPP enters the brain which disparate amyloids can cross-seed one another to reinforce 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 humour (CSF). These observations prompted us to explore a possible 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 gaggle with increased risk for both T2D and AD, peripheral IAPP levels weren't significantly different in samples with no disease, T2D, AD, or both T2D and AD. Furthermore, within the Tg 2576 AD mouse model, IAPP plasma levels weren't significantly elevated at an age where the mice exhibit the glucose intolerance of pre-diabetes. supported this data, it appears unlikely that peripheral IAPP cross-seeds Aβ pathology in AD brain. However, we offer evidence for a unique association between brain derived IAPP and AD, which suggests that brain derived IAPP plays a task in Aβ oligomerization and AD pathology. This potential connection, together with IAPP's known role in weight and state of mind, requires further research.

There is interest in "infectious" non-prion amyloid proteins, especially if such cross-seeding or "infection" underlies the mechanistic linkage between the extracellular amyloids of type 2 diabetes (T2D) and Alzheimer's disease (AD). There are several studies linking T2D and AD, indeed the link being described as diabetes of the brain, or type 3 diabetes. this idea relies on two known observations. First, that disparate amyloid proteins can cross-seed or catalyze each other's misfolding to reinforce pathology in neurodegenerative diseases, and such an interaction was first demonstrated in vitro, and recently in vivo. Second, several publications have demonstrated that amyloids are transmissible like infectious prions. However, the bulk of the above studies were concerned with brain-derived amyloids.

One obvious test of this "infectious" hypothesis would be to research the interaction of the extracellular amyloids of T2D and AD. Islet amyloid polypeptide (IAPP) is generated within the pancreas, co-secreted together with insulin from storage vesicles into the bloodstream, and forms extracellular amyloid deposits within the pancreatic islets in T2D. Amyloid β (Aβ) is that the amyloid protein that misfolds and accumulates as extracellular amyloid plaques in AD. We might expect that elevation of peripherally generated IAPP, as within the early stages of T2D, upon entering the brain could augment, crossed, or "infect" the misfolding of the brain-derived amyloid Aβ.

We formulated the hypothesis that islet amyloid polypeptide (IAPP) involved in T2D could cross-seed and augment Aβ misfolding to exacerbate AD pathology. However, so as for IAPP to play a job in AD pathology, we first needed to demonstrate several corollaries of this hypothesis: 1. IAPP is capable of entering the brain, 2. IAPP is in a position to misfold A, 3. IAPP is related to amyloid plaques, and 4. plasma levels of IAPP correlate with AD. For the primary corollary, there's increasing evidence supporting the presence of IAPP within the brain. IAPP, like insulin, is understood to be ready to cross the barrier, albeit it's been observed that a maximum of 0.11% of IAPP measured over only a 15 min fundamental measure crossed the barrier. Furthermore, IAPP immune-reactivity and receptors are demonstrated within the brain and in AD tissues. During the preparation of this manuscript, IAPP was identified in AD brain tissues by another laboratory, and two other reports suggest that IAPP enters the brain to change cognition. Equally important, and fewer well-known, is that IAPP may additionally be generated within the brain, as IAPP mRNA has been identified in AD brain tissues.

Second, IAPP augments Aβ misfolding. While IAPP interacts with Aβ, the literature of the consequences of IAPP on Aβ misfolding is sparse. a previous study indicated that IAPP didn't augment Aβ misfolding, however this study used high concentrations of pre-aggregated amyloids to judge fibril elongation. Per se cross-seeding of physiological concentrations of monomeric amyloids wasn't evaluated. A separate experimental study indicated that IAPP augmented Aβ oligomerization, and an in silico study demonstrates hetero-assembly of IAPP and Aβ into oligomers. These studies even have drawbacks, in silico might not reflect in vivo conditions, and therefore the former study failed to use a variety of IAPP competent to misfold to adopt an amyloid conformation. In contrast to the opposite studies, we used near-physiological concentrations of misfolding competent Aβ and IAPP, starting with the proteins in a very monomeric conformation. We must always mention that a recent publication suggest that IAPP may clear Aβ from the brain. Third, there's just one recent publication demonstrating the association of IAPP with amyloid plaques, published during the preparation of our manuscript. However, we are the primary reporting IAPP association with amyloid plaques in 2 mouse models of AD, likewise as in familial AD. Last and for the fourth corollary, there was no prior data correlating IAPP plasma levels with AD pathology, with two such studies only published during the preparation of this manuscript.

**Foot Note:** This work is partly presented at International Conference on Psychology, Autism and Alzheimer's disease September 30-October 01, 2013 at Hilton San Antonio Airport, TX, USA