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ALZHEIMER DISEASE

Misfolded diabetes-mellitus peptide seeds amyloid-β aggregation

> Our findings might provide an answer to the question of how AD and T2DM ... interact at the molecular level to promote each other

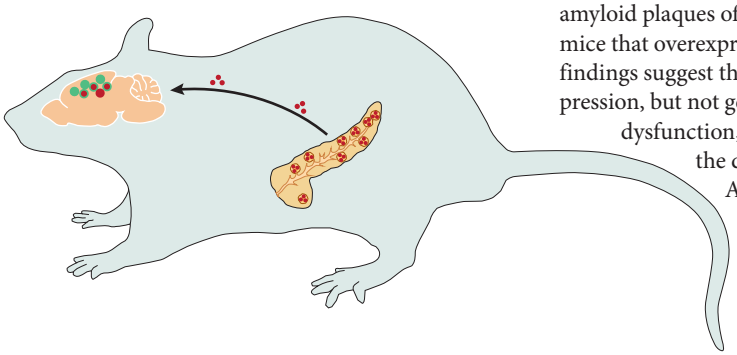
A misfolded protein present in type 2 diabetes mellitus (T2DM) can exacerbate the aggregation of amyloid-β (Aβ), according to new research.

An association has long been recognized between Alzheimer disease (AD) and T2DM. A high risk of dementia is observed in individuals with T2DM, and glucose intolerance is exhibited by the majority of patients with AD. However, the mechanisms underlying this association are unknown. Both diseases feature misfolding and aggregation of proteins, resulting in Aβ deposition in the brains of individuals with AD, and the aggregation of islet amyloid polypeptide (IAPP) within the pancreas in individuals with T2DM.

Ines Moreno-Gonzalez and colleagues hypothesized that aggregates of IAPP can cross-seed the aggregation of Aβ, thus mediating the link between AD and T2DM. The team showed that addition of preformed IAPP aggregates to $A\beta_{40}$ monomers *in vitro* accelerated misfolding of Aβ compared with unseeded Aβ monomers.

To investigate whether IAPP could also nucleate Aβ aggregation *in vivo*, the researchers crossed mice overexpressing human IAPP with mice expressing an amyloid precursor protein (*APP*) gene containing the Swedish mutation, which is known to cause early-onset AD.

Mice expressing both human IAPP and mutant APP had an increased Aβ burden in the hippocampus and cortex, compared with mice expressing mutant APP alone or APP-mutant mice injected with the β-cell toxin streptozotocin to induce diabetes mellitus. In addition, IAPP colocalized with Aβ in the amyloid plaques of the APP-mutant mice that overexpressed IAPP. These findings suggest that IAPP overexpression, but not general pancreatic dysfunction, exacerbates the deposition of Aβ plaques.



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Inoculation of APP-mutant mice with pancreatic homogenates from mice overexpressing human IAPP — but not from wild-type mice or mice with streptozotocin-induced diabetes mellitus — also resulted in increased Aβ burden in the cortex and hippocampus. Interestingly, IAPP-inoculated mice performed significantly worse than both control groups on the Barnes maze test for short-term memory.

"Our findings might provide an answer to the question of how AD and T2DM, two of the most common medical problems worldwide, interact at the molecular level to promote each other," concludes corresponding author Claudio Soto. The team are now turning their attention to human tissue, to determine whether evidence for cross-seeding between IAPP and Aβ can be detected in patients with AD and T2DM.

Charlotte Ridler

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