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A second amyloid may play a role in Alzheimer's disease, researchers find

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A protein secreted with insulin travels through the bloodstream and accumulates in the brains of individuals with type 2 diabetes and dementia, in the same manner as the amyloid beta Aβ plaques that are associated with Alzheimer's disease, a study by researchers with the UC Davis Alzheimer's Disease Center has found.

The study is the first to identify deposits of the protein, called amylin, in the brains of people with Alzheimer's disease, as well as combined deposits of amylin and plaques, suggesting that amylin is a second amyloid as well as a new biomarker for age-related dementia and Alzheimer's.

"We've known for a long time that diabetes hurts the brain, and there has been a lot of speculation about why that occurs, but there has been no conclusive evidence until now," said UC Davis Alzheimer's Disease Center Director Charles DeCarli.

"This research is the first to provide clear evidence that amylin gets into the brain itself and that it forms plaques that are just like the amyloid beta that has been thought to be the cause of Alzheimer's disease," DeCarli said. "In fact, the amylin looks like the amyloid beta protein, and they both interact. That's why we're calling it the second amyloid of Alzheimer's disease."

"Amylin deposition in the brain: A second amyloid in Alzheimer's disease?" is published online in the *Annals of Neurology*.

Type 2 diabetes is a chronic metabolic disorder that increases the risk for cerebrovascular disease and dementia, a risk that develops years before the onset of clinically apparent diabetes. Its incidence is far greater among people who are obese and insulin resistant.

Amylin, or islet amyloid polypeptide, is a hormone produced by the pancreas that circulates in the bloodstream with insulin and plays a critical role in glycemic regulation by slowing gastric emptying, promoting satiety and preventing post-prandial spikes in blood glucose levels. Its deposition in the pancreas is a hallmark of type 2 diabetes.

When over-secreted, some proteins have a higher propensity to stick to one another, forming small aggregates, called oligomers, fibrils and amyloids. These types of proteins are called amyloidogenic and include amylin and ??. There are about 28 amyloidogenic proteins, each of which is associated with diseases.

The study was conducted by examining brain tissue from individuals who fell into three groups: those who had both diabetes and dementia from cerebrovascular or Alzheimer's disease; those with Alzheimer's disease without diabetes; and age-matched healthy individuals who served as controls.

The research found numerous amylin deposits in the gray matter of the diabetic patients with dementia, as well as in the walls of the blood vessels in their brains, suggesting amylin influx from blood circulation. Surprisingly, the researchers also found amylin in the brain tissue of individuals with Alzheimer's who had not been diagnosed with diabetes; they postulate that these individuals may have had undiagnosed insulin resistance. They did not find amylin deposits in the brains of the healthy control subjects.

"We found that the amylin deposits in the brains of people with

dementia are both independent of and co-located with the A?, which is the suspected cause of Alzheimer's disease," said Florin Despa, assistant professor-in-residence in the UC Davis Department of Pharmacology. "It is both in the walls of the blood vessels of the brain and also in areas remote from the blood vessels.

"It is accumulating in the brain and we found signs that amylin is killing neurons similar to ??," he continued. "And that might be the answer to the question of 'What makes obese and type 2 diabetes patients more prone to developing dementia?'"

The researchers undertook the investigation after Despa and his colleagues found that amylin accumulates in the blood vessels and muscle of the heart. From this evidence, he hypothesized that the same thing might be happening in the brain. To test the hypothesis he received a pilot research grant through the Alzheimer's Disease Center.

The research was conducted using tissue from the brains of individuals over 65 donated to the UC Davis Alzheimer's Disease Center: 15 patients with Alzheimer's disease and type 2 diabetes; 14 Alzheimer's disease patients without diabetes; and 13 healthy controls. A series of tests, including Western blot, immunohistochemistry and ELISA (enzyme-linked immunosorbent assay) were used to test amylin accumulation in specimens from the temporal cortex.

In contrast with the healthy brains, the brain tissue infiltrated with amylin showed increased interstitial spaces, cavities within the tissue, sponginess, and blood vessels bent around amylin accumulation sites.

Despa said that the finding may offer a therapeutic target for drug development, either by increasing the rate of amylin elimination through the kidneys, or by decreasing its rate of oligomerization and deposition in diabetic patients.

"If we're smart about the treatment of pre-diabetes, a condition that promotes increased amylin secretion, we might be able to reduce the risk of complications, including Alzheimer's and dementia," Despa said.

Provided by UC Davis

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