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Study links diabetes and Alzheimer's disease

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Diabetic individuals have a significantly higher risk of developing Alzheimer's disease but the molecular connection between the two remains unexplained. Now, researchers at the Salk Institute for Biological Studies identified the probable molecular basis for the diabetes – Alzheimer's interaction.

In a study published in the current online issue of *Neurobiology of Aging*, investigators led by David R. Schubert, Ph.D., professor in the Cellular Neurobiology Laboratory, report that the blood vessels in the brain of young diabetic mice are damaged by the interaction of elevated blood glucose levels characteristic of diabetes and low levels of beta amyloid, a peptide that clumps to form the senile plaques that riddle the brains of Alzheimer's patients.

Although the damage took place long before the first plaques appeared, the mice suffered from significant memory loss and an increase in inflammation in the brain. "Although the toxic beta amyloid peptide was first isolated from the brain blood vessels of Alzheimer's patients, the contribution of pathological changes in brain vascular tissue to the disease has not been well studied," says Dave R. Schubert, Ph.D., professor and head of the Cellular Neurobiology Laboratory. "Our data clearly describe a biochemical mechanism to explain the epidemiology, and identify targets for drug development."

Alzheimer's and diabetes are two diseases that are increasing at an alarming rate within the U.S. population. Alzheimer's affects one in 10 Americans over 65 years of age and nearly 50 percent of those over 85

years old. Similarly, 7 percent or approximately 20 million Americans have diabetes, with the vast majority of these individuals being over 60.

Recent epidemiological studies have shown that diabetic patients have a 30 to 65 percent higher risk of developing Alzheimer's disease compared to non-diabetic individuals. The increased risk applies to both type 1 and type 2 diabetes, which share hyperglycemia as a common pathogenic factor.

"Many studies have focused on altered insulin signaling in the brain as a possible mechanism for the association between Alzheimer's disease and diabetes but researchers paid much less attention to the direct affects of increased blood glucose levels on brain function and the pathogenesis of Alzheimer's," explains lead author Joseph R. Burdo, Ph.D., a former postdoctoral researchers in Schubert's lab and now an assistant professor at Bridgewater State College in Bridgewater, Massachusetts.

To get at the bottom of the question why diabetes predisposes people to Alzheimer's disease as they age, the Salk researchers Schubert, Burdo and Qi Chen, in collaboration with diabetes expert Nigel Calcutt, a professor in UCSD's Department of Pathology, induced diabetes in young mice, whose genetic background predisposes them to acquire the symptoms of Alzheimer's with old age.

These mice suffered damage to blood vessels well before any overt signs of Alzheimer's disease such as nerve cell death or the acquisition of amyloid deposits, the hallmark of the disease, could be detected in their brains. Further experiments revealed that the vascular damage was due to the overproduction of free radicals, resulting in oxidative damage to the cells lining the brain's blood vessels.

"While all people have a low level of amyloid circulating in their blood, in diabetics there may be a synergistic toxicity between the amyloid and

high level of blood glucose that is leading to the problems with proper blood vessel formation," says Burdo.

An earlier study by Schubert and his team has revealed that the exposure of cells to amyloid causes free radical production prompting a clinical trial investigating whether the antioxidant and free radical scavenger vitamin E would be beneficial for the treatment of Alzheimer's disease.

While this initial trial was only marginally successful, ongoing work in Schubert's lab centers on a new family of drugs that has shown promise for preventing Alzheimer's disease and perhaps the vascular damage associated with diabetes.

Source: Salk Institute