

Researchers discover novel mechanisms that might causally link type-2 diabetes to Alzheimer's disease

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A recent study by Mount Sinai faculty suggests that a gene associated with onset of type-2 diabetes also decreases in Alzheimer's disease dementia cases. The research, led by Dr. Giulio Maria Pasinetti, MD, Ph.D., The Aidekman Family Professor in Neurology, and Professor of Psychiatry and Geriatrics and Adult Development at Mount Sinai School of Medicine, was published this week in the scientific journal, *Archives of Neurology*.

"This new evidence is of extreme interest," Dr. Pasinetti tells us, "especially because of the evidence that approximately 60% of Alzheimer's disease [dementia](#) cases have at least one serious medical condition primarily associated with [type-2 diabetes](#), a chronic condition which includes high blood glucose content (hyperglycemia) and reduced sensitivity to [insulin](#), among other conditions."

"The relationship between type-2 diabetes and Alzheimer's disease is elusive," says Dr. Pasinetti. Not all subjects with type-2 diabetes are affected by Alzheimer's disease, and similarly, not all Alzheimer's disease cases are diabetic. However, in the last few years, epidemiological evidence indicates that, relative to healthy elderly subjects, people of the same age affected by type-2 diabetes are twice as likely to develop Alzheimer's disease dementia. The reason is not known. The new study from Dr. Pasinetti, reported in this week's issue of *Archives of Neurology*, provides insight into a potential mechanism that

might explain the relationship between type-2 diabetes and Alzheimer's disease onset and progression.

Dr. Pasinetti and colleagues found that a gene known as proliferator-activated receptor coactivator 1 - (PGC-1), a key regulator of glucose content currently investigated as a potential therapeutic target for type-2 diabetes, is also decreased in Alzheimer' disease dementia cases. Most importantly, Dr. Pasinetti reports that PGC-1 decreased in Alzheimer' disease dementia cases with progression of the clinical disease and positively correlates with brain accumulation of β -amyloid, an abnormal protein highly linked to Alzheimer' disease dementia and brain degeneration. This evidence is of high interest to the field and suggests, for the first time, a strong relationship between decreased content of a gene responsible for type-2 diabetes in Alzheimer's disease dementia cases, says Dr. Pasinetti.

"Of considerable interest," continues Dr. Pasinetti, "is the evidence found in further mechanistic studies in our laboratory, indicating that promoting PGC-1 content in brain cells, using a transgenic mouse model of Alzheimer's disease, attenuates hyperglycemic-mediated production of β -amyloid, highly linked to Alzheimer' disease dementia. These findings are very exciting, and for the first time tentatively link type-2 diabetic metabolic defects to increasing dementia mediated by β -amyloid production."

The discovery in Dr. Pasinetti's laboratory has staggering societal implications: there are currently more than 5 million Americans affected by Alzheimer's disease dementia, and the disease incidence is expected to skyrocket in the three decades as the population ages. The question now is how we can translate this evidence into the development of novel approaches for disease prevention and treatment.

Dr. Pasinetti and his colleagues are optimistic that if they find that

PGC-1 α can be manipulated pharmacologically, these studies will provide important insights to be used in the formulation of novel treatments and possible preventative strategies in Alzheimer's disease.

Source: Mount Sinai School of Medicine

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