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New type 2 diabetes research paves the way for future Parkinson's treatments

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If you suffer from type 2 diabetes, you run a higher risk of being affected by Parkinson's disease. Chalmers researchers have now found a possible cause. The findings might lead to new future drugs.

The connection between type 2 diabetes and Parkinsons's in patients is previously known. A person with type 2 diabetes have a higher risk of also getting Parkinsons's disease, but not the other way round. But why?

Proteins are the body's work horses and they are the molecular machines that perform all the tasks in our cells. A protein is a long chain of amino acids that have to fold into a specific three-dimensional structure in order to function. But sometimes folding goes wrong, and instead the chain misfolds or aggregates with other chains, which can lead to a number of different diseases.

Parkinson's and type 2 diabetes, as well as Alzheimer's disease, is caused by proteins that behave in a way that they are not supposed to. They aggregate with each other into long fibers, amyloids, that harm the cells.

Professor Pernilla Wittung-Stafshede and the researcher Istvan Horvath, both working in the division of Chemical Biology at the Department of Biology and Biotechnical Engineering, have studied the two protein chains connected with Parkinson's disease and type 2 diabetes, respectively. Wittung-Stafshede and Horvath discovered that the two proteins affect each other's aggregation reactions into amyloid fibers. This cross-reactivity between the proteins provide an explanation for the

observed link between the diseases.

"The diabetes protein can make the Parkinson's-protein aggregate faster," Pernilla Wittung-Stafshede explains.

"It's actually strange that no one had done these experiments before. To us, they were obvious to do. Our findings underline the importance of more studies of the consequences of binding events between different, unrelated, proteins in the body. Human cells contains of many thousands of different proteins, which means up to 40 percent of the cell volume is occupied. The crowded environment makes the risk greater that the "wrong" proteins may meet and cross-react."

The specific protein that misfolds and cause type 2 diabetes is called amylin and aggregates in the pancreas. The Parkinson's-protein is called alpha-synuclein and acts in the brain. But alpha-synuclein is also found in the pancreas, and amylin has been identified in the brain; thus it's not unlikely that the two proteins would meet and affect each other in vivo.

The scientists looked at many combinations of two variants of amylin and alpha-synuclein and taken together, the results pointed to a common trend. It seemed that amyloid fibers from fast-aggregating proteins made more slowly-aggregating proteins form amyloids faster, while amyloid fibers from slowly-aggregating proteins made faster-aggregating proteins form amyloids slower.

"It's important to understand the steps of disease progression on a mechanistic and molecular level. Otherwise we might never understand what part of the reactions to target in order to limit the disease. With more basic knowledge of what initiates amyloid diseases like Parkinson's, it will be possible to design new drugs that target already the early stages of disease."

The article with Pernilla Wittung-Stafshede's and Istvan Horvath's study was recently published in the journal *PNAS* (*Proceedings of the National Academy of Sciences*) and received very positive feedback from the reviewers:

"Yes, it was great! Many times you get a lot of critique and additional experiments to perform. Here, we used established methods for our experiments so it was the scientific question we asked that was the novelty," Pernilla Wittung-Stafshede concludes.

Provided by Chalmers University of Technology