'Alzheimer protein' seems to slow down neurotransmitter production

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Researchers report how abnormal protein deposits in the brains of Alzheimer's patients disrupt the signaling between nerve cells. They varied the amount of APP protein and related proteins associated with Alzheimer's disease in cell cultures, and then analyzed how this manipulation affected other proteins in the cell. The result: The amount of APP present was related to the amount of an enzyme that is essential for the production of neurotransmitters and therefore for communication amongst nerve cells.

How abnormal protein deposits in the brains of Alzheimer's patients disrupt the signalling between nerve cells has now been reported by researchers in Bochum and Munich, led by Dr. Thorsten Müller from the Medizinisches Proteom-Center of the Ruhr-Universität, in the journal *Molecular and Cellular Proteomics*. They varied the amount of APP protein and related proteins associated with Alzheimer's disease in cell cultures, and then analysed how this manipulation affected other proteins in the cell. The result: the amount of APP present was related to the amount of an enzyme that is essential for the production of neurotransmitters and therefore for communication amongst nerve cells.

Proteomics: analysing all the proteins of the cells at once

Amyloid plaques are a characteristic feature of Alzheimer's disease. They consist largely of cleavage products of the so-called amyloid

precursor protein APP, which occur in excess in the brains of Alzheimer's patients. What role APP plays in healthy people and why the abnormal accumulation of amyloid disrupts the regular functioning of the brain is still largely unclear. To understand the function of APP, the RUB researchers established a new cell model. The new cells produced only a very small amount of APP. What impact this had on all the other proteins of these cells was examined by the researchers through the use of mass spectrometry, among other things. With this method they identified over 2000 proteins and determined their concentrations. They were looking specifically for molecules whose concentrations in the newly established low-APP cells were different than in the reference cells that contained normal amounts of APP.

Abnormal protein able to curb neurotransmitter production

"One candidate has particularly caught our attention, this being the enzyme methionine adenosyltransferase II, alpha, MAT2A for short", Thorsten Müller said. Among other things, the enzyme is crucially involved in the production of neurotransmitters. Low-APP cells contained less MAT2A than the reference cells. To confirm the connection between the "Alzheimer's protein" APP and the neurotransmitter-producing MAT2A, the team studied tissue samples from the brains of deceased Alzheimer's patients and from healthy individuals. In the tissue of the Alzheimer's patients there was less MAT2A than in the healthy samples. These results suggest that APP and MAT2A concentrations are related and are linked to the synthesis of neurotransmitters. "Our results point to a new mechanism by which the defective cleavage of the APP protein in Alzheimer's disease could be directly related to altered neurotransmitter production", Müller said. "As a result, the signal transduction of nerve cells could be disrupted, which, over an extended period, could possibly also cause the death of cells."

More information: A. Schrötter, K. Pfeiffer, F. El Magraoui, H. Platta, R. Erdmann, Helmut E. Meyer, R. Egensperger, K. Marcus, T. Müller (2012): The APP family members are key players in S-adenosylmethionine formation by MAT2A and modify BACE1 and PSEN1 gene expression - relevance for Alzheimer's disease, *Molecular and Cellular Proteomics*, doi: 10.1074/mcp.M112.019364