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Diabetes drug could work against Alzheimer's

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Scientists from Berlin, Bonn and Dundee show in animal models that the diabetes drug metformin has an effect against one of the main causes of the Alzheimer's disease.

Metformin, a drug used in type 2-diabetes might have the potential to also act against Alzheimer's disease. This has been shown in a study from scientists of the German Center for Neurodegenerative Diseases (DZNE), the University of Dundee and the Max-Planck-Institute for Molecular Genetics. The researchers have found out that the diabetes drug metformin counteracts alterations of the cell structure protein Tau in mice nerve cells. These alterations are a main cause of the Alzheimer's disease. Moreover, they uncovered the molecular mechanism of metformin in this process. "If we can confirm that metformin shows also an effect in humans, it is certainly a good candidate for an effective therapy on Alzheimer's diseases," says Sybille Krauß from DZNE. Their results have been published in the scientific journal *PNAS* on November 22nd.

Alzheimer's disease is a form of dementia that affects almost exclusively elderly people. Today, about 700,000 people are suffering from Alzheimer's disease in Germany. Neurons in their brains die, leading to cognitive impairment. At the molecular level, the disease is characterized amongst others by the formation of Tau protein deposits in nerve cells. Tau is a molecule that usually binds to the supportive cytoskeleton and performs a function in the transport system of the cell. In Alzheimer's disease, Tau is tipped too strongly with phosphate groups.

This phosphorylation causes removal of Tau from the cytoskeleton and aggregation.

To counteract this problem, researchers aimed at regulating the protein PP2A. This protein is normally responsible for removing phosphate groups from Tau protein. In Alzheimer's disease, PP2A is not active enough – leading to an increased phosphorylation and deposition of Tau. The scientists around Sybille Krauss and Susann Schweiger (University of Dundee) therefore looked for a drug that increases the activity of PP2A. "So far there is no drug on the market that targets the formation of tau aggregates," says Krauß.

In cell culture experiments with mouse nerve cells, the researchers showed that metformin directly protects PP2A against degradation by preventing the binding to special degradation proteins. This mechanism of metformin has been unknown so far. In addition, an increase in PP2A activity leads to a reduction in Tau phosphorylation. In a next step, the scientists added metformin to drinking water of healthy mice. This also led to a reduction of Tau-phoshorylation in brain cells. In further experiments, the researchers now intend to investigate, whether metformin prevents the deposition of tau proteins also in mouse models of Alzheimer's disease and improves cognitive performance of the animals. The effect in humans will then be tested in clinical studies. There is no risk of unexpected side effects, due to the fact that the drug is already used against diabetes.

More information: Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, Sharkey J, Williamson R, Fuchs M, Köhler A, Glossmann H, Schneider R, Sutherland C, Schweiger S: The Biguanide metformin acts on tau phosphorylation via mTOR/PP2A signalling. *PNAS* published ahead of print November 22, 2010, doi:10.1073/pnas.0912793107