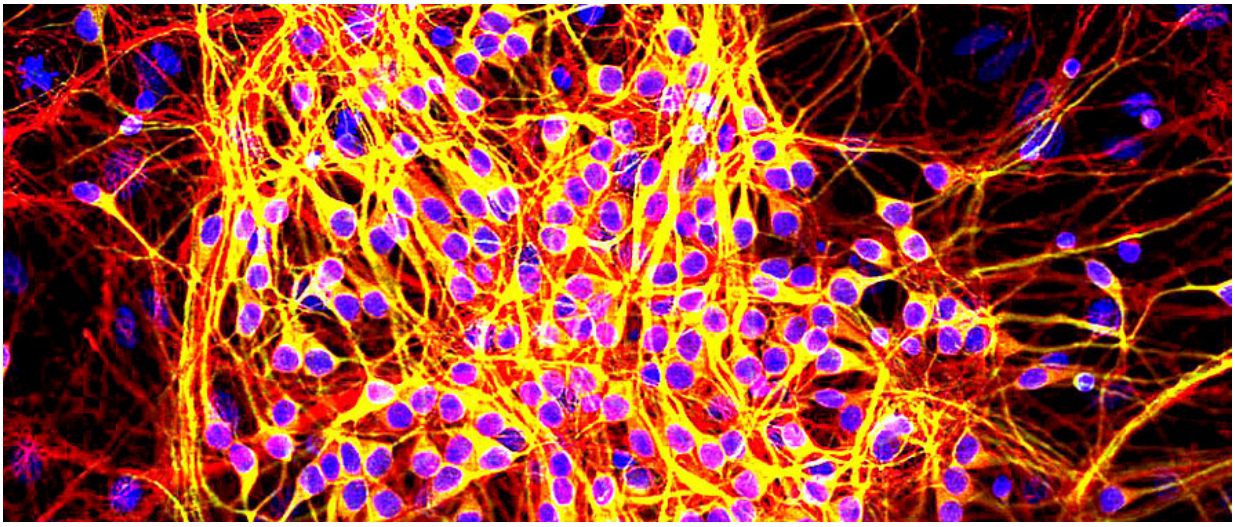
Could diabetes drugs curb our dementia epidemic?

March 28 2017, by Gary Finnegan, From Horizon Magazine



There may be a connection between tau proteins, which are linked to Alzheimer's, and insulin resistance. Credit: 'MAP2-tau in neurons' by GerryShaw is licensed under CC BY-SA 4.0

People with lifestyle-related diabetes are at an increased risk of developing dementia and, with both conditions on the rise, scientists are scrambling to understand their connection in the hope of finding new treatments.

There are 54 million people in Europe living with lifestyle-related – or Type 2 – diabetes and the numbers are soaring, fuelled by the obesity

epidemic. Alzheimer's, the most common form of dementia, affects around 10.5 million Europeans and this number is forecast to hit 18.7 million by 2050 as a result of population ageing.

People with Type 2 diabetes have higher levels of sugar in their blood because their cells have become resistant to insulin which normally regulates blood sugars. Insulin resistance in the brain has been linked to dementia in large, long-term studies but the exact mechanism behind the phenomenon is still being teased out.

"There is growing evidence from epidemiological studies suggesting that Type 2 diabetes is a risk factor for dementia, particularly Alzheimer's disease," said Dr Shreyasi Chatterjee at the University of Southampton, UK. "Therefore, we want to know more about the relationship between insulin resistance seen in diabetes and the protein build-up associated with Alzheimer's."

Protein tangles

Key to solving these puzzles are two proteins associated with memory loss in Alzheimer's – amyloid-beta, which accumulates in plaques that trigger brain cell death, and tau proteins, which cause tangles in the brain.

"Insulin resistance in the brain can make it difficult for Alzheimer's patients to process the sugar which is needed to fuel brain cells," said Dr Chatterjee. "It disrupts normal signalling pathways in the brain and can also hamper the brain's natural mechanism for clearing misfolded proteins that trigger memory loss."

As part of the EU-funded AlzDiabetes project, Dr Chatterjee is focusing on the role of tau proteins in fruit flies that have been genetically programmed to mimic the kind of neurodegeneration seen in

Alzheimer's disease.

Fruits flies are often used in genetic research as they have around 75 % of the genes that cause human disease and they are easy to work with thanks to their short breeding times. Dr Chatterjee worked with a population of fruit flies bred to have excessive tau proteins, and experimented with adding insulin receptor substrate (IRS) – a key player in processing insulin.

She found that adding IRS gave the fruit flies better memories and longer lifespans, whereas knocking out the gene that produces it increased the level of tau proteins. This new observation is the most direct evidence to date of a direct connection between insulin resistance seen in diabetes and the tau tangles seen in Alzheimer's disease.

Her team also observed that when the flies were insulin resistant their brains were unable to clear away the toxic tau proteins, providing an explanation of why people with Type 2 diabetes might develop Alzheimer's.

Curbing dementia risk

As scientists learn more about how insulin resistance affects the brain, researchers hope that controlling blood sugar in diabetic patients will curb their dementia risk.

"We already know that treating Alzheimer's disease with inhaled insulin (a diabetes medication) reduces cognitive impairment," said Dr Chatterjee. "Other diabetes drugs are now in clinical trials to test whether they could slow the progression of dementia."

In addition to having a higher risk of Alzheimer's, diabetes patients are also more likely than the average person to develop Parkinson's disease.

Professor Yifat Miller at the Ben-Gurion University of the Negev in Israel has explored the relationship between diabetes, Alzheimer's and Parkinson's as part of the EU-funded AbetaAlphasynTau project.

Her team used computer simulations to model the interactions at the molecular level between the amyloid-beta protein, which is associated with Alzheimer's, alpha-synuclein, which builds up in the brains of Parkinson's patients, and amylin, a hormone produced by the pancreas. The project pinpointed crucial fragments of these proteins that make them stickier when they interact.

"We are now developing molecules that would inhibit these interactions," Prof. Miller said. "The new molecules will prevent the interactions between these proteins so that they will not clump together. Consequently, we could reduce the likelihood that people with Type 2 diabetes will develop Alzheimer's and Parkinson's later in life."

Using their detailed molecular knowledge of these brain diseases, Prof. Miller's team is designing molecules that could break the link between these three diseases. However, this is still in the early stages of drug design and several new medicines may be needed.

"The inhibitor we are working on is not a single molecule but a cocktail of molecules," she said. "It's very challenging but we are excited about laying the foundation for understanding how these diseases are connected."

Horizon brings you the latest news and features about thought-provoking science and innovative research projects funded by the EU. Our articles are written by independent science journalists and are designed to appeal to both scientists and non-scientists alike.

Provided by Horizon: The EU Research & Innovation Magazine