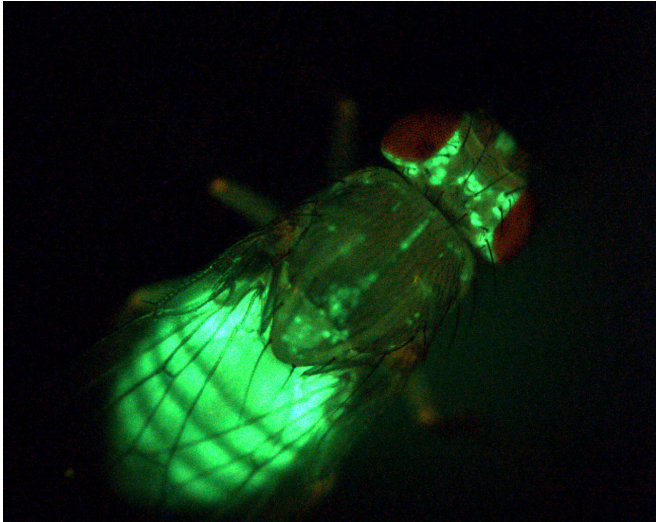


Are high blood glucose levels an effect rather than the cause of diabetes?

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Flies are an established model to study energy metabolism. The body fat of this fly is labelled with GFP ("green fluorescent protein"). Credit: The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ)

Insulin resistance and elevated blood glucose levels are considered to be the cause of type 2 diabetes. However, scientists from the German Cancer Research Center (DKFZ) and Heidelberg University Hospital have now provided evidence that things might be completely different. They showed in flies that elevated levels of the metabolite MG (methylglyoxal) cause the typical diabetic disturbances of the metabolism and lead to insulin resistance, obesity and elevated blood sugar levels.

Type 2 diabetes, a form of diabetes with a typical onset in middle or older age, causes severe health complications including elevated risks for heart disease and strokes, massive blood flow problems in the legs as well as severe damage to eyes, nerves and kidneys. These dangerous late effects are believed to be caused by high [blood sugar](#)

[levels](#), which develop when the body cells no longer respond to [insulin](#), the regulatory hormone that lowers blood sugar.

Blood [glucose](#) levels correlate with the level of diabetic symptoms. When very high [blood glucose levels](#) are lowered using drugs, the rate of infarctions and strokes as well as blood flow problems decrease in parallel.

"But this holds true only up to a certain point," said Peter Nawroth, Medical Director of the Department of Endocrinology and Metabolism at Heidelberg University Hospital. "Large clinical trials in recent years have shown: Even when blood sugar could be lowered by drugs below the diabetes threshold value, many patients nevertheless developed typical diabetic damage to nerves and kidneys. This suggests that type 2 diabetes might in fact have molecular causes that are independent of insulin and glucose."

Peter Nawroth and Aurelio Teleman, who leads the Division of Signal Transduction in Cancer and Metabolism at the German Cancer Research Center (DKFZ) in Heidelberg, knew that in type 2 diabetics, high levels of a glucose metabolite called methylglyoxal (MG) have been observed. Medics have thought so far that this is an effect of elevated [blood](#) glucose levels. Since MG can cause damage to proteins, textbook knowledge consequently holds that it must be one of the culprits in causing typical diabetic damage. However, in light of their recent results, metabolism experts Teleman and Nawroth have now doubted this sequence of events.

When rats are given MG with their food, they develop many typical signs of diabetes, including [insulin resistance](#). The Heidelberg researchers planned to investigate the effects of long-term elevated MG concentrations on the organism. They chose fruit flies as a model for this purpose. "Flies and humans are not very closely related. However, since energy metabolism developed very early on

in evolution, results are nevertheless meaningful and can usually be translated to mammals and humans," said Teleman.

Using genetic engineering, the researchers turned off the enzyme that breaks down MG in flies. The glucose metabolite MG subsequently accumulated in their bodies. The flies soon developed insulin resistance. Later, they became obese and at higher age their glucose levels also became disrupted.

"It appears to be sufficient to increase the MG level to trigger insulin resistance and typical diabetic metabolic disturbances," Teleman resumes. "This is clear evidence that MG is not the consequence but rather the cause of type 2 [diabetes](#)."

This observation, in turn, raises the question about what might cause an elevated MG level. For example, obese people who are not diabetic also display elevated MG levels. "Why this is so, we don't know. This is an important aspect of our future research," said Nawroth. Teleman adds: "Production as well as decomposition of MG is influenced by numerous metabolic processes which we do not know yet and have to understand better. And we also urgently plan to study in mice which clinical symptoms long-term elevated MG levels cause in mammals."

More information: Alexandra Moraru, Janica Wiederstein, Daniel Pfaff, Thomas Fleming, Aubry K. Miller, Peter Nawroth und Aurelio A. Teleman: Elevated Levels of the Reactive Metabolite Methylglyoxal Recapitulate Progression of Type 2 Diabetes, *Cell Metabolism* 2018, [DOI: 10.1016/j.cmet2018.02003](#)

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