Clever gene construct combats metabolic syndrome

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Tastes nice but is unhealthy: anyone who makes a habit of eating fast food and does not do enough exercise can expect various symptoms of metabolic syndrome, such as high blood pressure, obesity and diabetes. Credit: SteFou!/Flickr

(Medical Xpress)—Researchers under ETH-Zurich professor Martin Fussenegger have created a new genetic network that could cure the

various symptoms of so-called metabolic syndrome in one fell swoop. It already works in mice.

Too much of the wrong food and not enough exercise: sooner or later, an increasing number of people in industrial nations pay the price for their lifestyle. High blood pressure, changed blood fat values, insulin resistance as a precursor to diabetes, and abdominal fat are characteristic of metabolic syndrome, the 'killer of the twenty-first century'. After all, it is the major risk factor for the development of coronary heart diseases. Today, many more people die of cardiovascular diseases worldwide than from cancer.

Until now, however, there has not been a holistic therapy for metabolic syndrome. Medicine diagnoses and treats every single symptom of metabolic syndrome separately. "However, all these diseases are linked," says ETH-Zurich professor Martin Fussenegger from the Department of Biosystems in Basel. His research group has now found an approach that could treat all the symptoms of metabolic syndrome at once.

Antihypertensive drug triggers cascade

The biotechnologists have constructed a synthetic signaling cascade from different biological molecules that can be triggered with the antihypertensive drug guanabenz and controlled based on the dosage. After the start signal, a chain reaction is set in motion in the cell and culminates with the production of a "super hormone" in the cell nucleus. This includes GLP1, which is connected to leptin via a molecular bridge. GLP1 reduces the blood sugar level; leptin inhibits the feeling of hunger and thus plays a key role in regulating the lipid metabolism.

The combination of the drug guanabenz, which has already been approved for clinical use, and the 'super hormone' produced by the synthetic signal cures all three key diseases associated with metabolic

syndrome at the same time.

The researchers tested their network in a model experiment using diabetic, obese mice suffering from high blood pressure. The animals lack the satiety hormone leptin so are always hungry and eat more than is good for them. The ETH-Zurich biotechnologists inserted an implant with ten million cells, each of which contained the synthetic signalling pathway, into the mice.

Construct successful in mice

The animals responded very well to the dose of guanabenz: the GLP1 and leptin concentration rose dramatically and twenty-four hours after the drug was dispensed insulin secretion also increased on account of the GLP1 content. After only three days, the level of cholesterol and other free fatty acids in the blood dropped – a good sign that the animals were beginning to recover from metabolic syndrome. Free guanabenz even lowered the blood pressure, too.

"This application is also realistic for the treatment of metabolic syndrome in humans," Fussenegger predicts. GLP1 is already administered as an alternative to insulin in the battle against diabetes. Leptin, on the other hand, would have to be substituted with another hormone that has a similar effect. "Leptin has failed to live up to its hopes as a therapeutic agent against obesity, as obese patients have sufficient leptin but have grown resistant to it," stresses the ETH-Zurich professor. However, he is confident that they can incorporate an alternative satiety hormone into their network. They merely used leptin to demonstrate the principle. It works perfectly well in mice.

In planning and constructing this network, the researchers were able to fall back on the Fussenegger group's existing expertise. The ingenious scientists had already assembled gene networks for diabetes or gout with

similar biological components, the properties of which are renowned. "But we only discovered that the antihypertensive drug guanabenz can be used as a start button by chance," says the ETH-Zurich professor from Basel.

Even though he is convinced that a gene construct designed in this way could treat metabolic syndrome with its array of symptoms, for the time being Fussenegger is reluctant to make any promises as to when a corresponding product might hit the market.

More information: Ye H, Charpin-El Hamri G, Zwicky K, Christen M, Folcher M, Fussenegger M. Pharmaceutically controlled designer circuit for the treatment of the metabolic syndrome. *PNAS* online, doi: 10.1073/pnas.1216801110

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