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Press Release

ETH Zurich researchers are developing an implantable device

Sensitive acid sensor controls insulin production

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ETH Zurich researchers from the Department of Biosystems Science and Engineering (D-BSSE) in Basel have developed an implantable device that precisely monitors acid build-up in the body for people with diabetes and produces insulin if acidosis becomes a risk.

Many human metabolic functions only run smoothly if the acid level in the body remains neutral and stable. For humans, normal blood pH values lie between 7.35 and 7.45. By way of comparison, an empty stomach is extremely acidic, with a pH value of 1.5.

The body constantly monitors this narrow pH band and quickly restores the ideal pH values in the event of any deviations. This is because many proteins cease to function properly if fluids in the body become even slightly more acidic. These proteins become unstable and alter their structure or interactions with other proteins, causing entire metabolic pathways to break down.

People with type 1 diabetes are particularly at risk of high acid levels. Their bodies produce no insulin, the hormone that regulates blood sugar levels, so their cells cannot absorb any glucose from the blood and have to tap into another energy source: fat reserves. In doing so, the liver produces beta-hydroxybutyrate, an acid which supplies the muscles and brain with energy via the bloodstream. If the body continues to use fat reserves for energy, however, this produces so much acid that the blood's pH value plummets while the sugar molecules circulate in the blood unused. If the lack of insulin is not noticed or treated in time, people with type 1 diabetes can die from ketoacidosis – metabolic shock resulting from an excess of beta-hydroxybutyrate.

Sensor measures acidity

A team of bioengineers from ETH Zurich's Department of Biosystems Science and Engineering (D-BSSE) in Basel have now developed a new implantable molecular device composed of two modules: a sensor that constantly measures blood pH and a gene feedback mechanism that produces the necessary amount of insulin. They constructed both modules from biological components, such as various genes and proteins, and incorporated them into cultivated renal cells. The researchers then embedded millions of these customised cells in capsules which can be used as implants in the body.

The heart of the implantable molecular device is the pH sensor, which measures the blood's precise acidity and reacts sensitively to minor deviations from the ideal pH value. If the pH values falls below 7.35, the sensor transmits a signal to trigger the production of insulin. Such a low pH value is specific for type 1 diabetes: although blood pH also drops due to alcohol abuse or exercise on account of the overacidification of the muscles, it does not fall below 7.35. The hormone insulin ensures that the normal cells in the body absorb glucose again and switch from fat to sugar as their energy source for metabolism, and the pH value rises again as a result. Once blood pH returns to the ideal range, the sensor turns itself off and the reprogrammed cells stop producing insulin.

Insulin level back to normal
The researchers have already tested their invention on mice with type 1 diabetes and related acidosis. The results look promising: mice with the capsules implanted produced the amount of insulin appropriate to their individual acid measurements. The hormone level in the blood was comparable to that of healthy mice that regulated their insulin levels naturally. The implant also compensated for larger deviations in blood sugar.

"Applications for humans are conceivable based on this prototype, but they are yet to be developed," says Martin Fussenegger. "We wanted to create a prototype first to see whether molecular prostheses could even be used for such fine adjustments to metabolic processes," he says. Preparing a product like this for the market, however, is beyond the scope of his institute's staff and financial resources, Fussenegger says, and would thus have to be pursued in collaboration with an industrial partner.

Extensive experience in metabolic diseases
Researchers in Fussenegger's group have already made headlines several times with similar synthetic networks. For instance, they developed an implant with genes that could be activated with blue light, thereby producing GLP-1, which regulates insulin production. They also put together a network that eliminates metabolic syndrome, a process set in motion by an authorised blood-pressure medicine. All of these networks respond to a signal and produce a hormonally active substance. The special thing about the new feedback mechanism, however, is that the body itself produces the signal, which is then detected by a sensor that triggers a fine-tuned therapeutic reaction.

Three groups from the D-BSSE worked on the present project. Fussenegger's group developed the genetic network; Professor of Biosystems Engineering Andreas Hierlemann and his team tested the acidity sensor with the aid of microfluidic platforms; and Jörg Stelling, a professor of computational systems biology, modelled it in order to estimate the dynamics of the insulin production.

Reference
Ausländer D, Ausländer S, Charpin-El Hamri G, Sedlmayer F, Müller M, Frey O, Hierlemann A, Stelling J, Fussenegger M. A synthetic Multifunctional Mammalian pH Sensor and CO2 Transgene-Control Device. Molecular Cell. Published online 10th July 2014. DOI: 10.1016/j.molcel.2014.06.007→

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