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Chronically elevated blood sugar levels disable 'fasting switch'

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Continually revved up insulin production, the kind that results from overeating and obesity, slowly dulls the body's response to insulin. As a result, blood sugar levels start to creep up, setting the stage for diabetes-associated complications such as blindness, stroke and renal failure. To make matters even worse, chronically elevated blood sugar concentrations exacerbate insulin resistance.

The vicious circle gets rolling, researchers at the Salk Institute for Biological Studies discovered, when out-of-control blood sugar levels disable the molecular switch that normally shuts off sugar production in the liver in response to rising levels of insulin.

Their findings, published in the March 7 issue of *Science* suggest that appropriate inhibitors of the enzymatic pathway that blocks the "sugar-off"-switch might be useful in lowering glucose levels in diabetic individuals and reducing long-term complications associated with the disease.

"The islet cells in the pancreas can compensate with increased insulin production only for so long when confronted with chronic obesity and inactivity," says Marc Montminy, Ph.D., a professor in the Clayton Foundation Laboratories for Peptide Biology, who led the study. "As a result glucose levels start to rise causing a host of problems."

Just like a flex-fuel vehicle that can run on either gasoline or ethanol, the human body can switch between different types of fuel: During the day

the body mostly burns glucose, and during the night or prolonged fasting, it burns primarily fat. But neither flex-fuel engines nor human brains can run on ethanol or fat alone —a little bit of gasoline or glucose needs to be thrown into the mix to keep either one of them humming.

Three years ago, Montminy discovered a “fasting switch” called CRTC2 (formerly known as TORC2) that flips on glucose production in the liver when blood glucose levels run low during the night. After a meal, the hormone insulin normally shuts down CRTC2 ensuring that blood sugar levels don’t rise too high.

In many patients with type II diabetes, however, CRTC2 no longer responds to rising insulin levels and as a result the liver acts like a sugar factory on overtime, churning out glucose throughout the day, even when blood sugar levels are high. The Salk researchers were interested in the molecular mechanism that leads to the breakdown of the normally tightly regulated feedback loop.

Mice whose livers light up — courtesy of the luciferase gene, which produces the glow in fireflies — as soon as CRTC2 is turned on, led post-doctoral fellow and first author Renaud Dentin, Ph.D., onto the trail of the hexosamine biosynthetic pathway. Activation of the pathway promotes the addition of sugar molecules to proteins, a process also known as O-glycosylation. “It had been known that increases in the concentration of circulating glucose activate the hexosamine biosynthetic pathway,” says Dentin. “But we had no idea that the resulting O-glycosylation would lock CRTC2 in the ‘on’-position.”

Normally, the rise in insulin after a meal activates a liver enzyme called SIK2. The enzyme chemically tags CRTC2 with a phosphate group, marooning the protein outside the cell’s nucleus. Unable to reach the genes involved in gluconeogenesis, CRTC2 is powerless to turn them on and glucose production in the liver ceases.

In the presence of excessive glucose levels, however, the hexosamine biosynthetic pathway is activated and blocks crucial phosporylation sites on CRTC2 by adding sugar molecules instead. CRTC2 can no longer be phosphorylated in response to rising insulin levels and is now free to slip into the nucleus and keep the gluconeogenic program going.

Shutting down the O-glycosylation pathway should then get the body's own glucose production under control, the researchers reasoned. Just as predicted, glucose tolerance and insulin sensitivity markedly improved in insulin resistant diabetic mice and mice fed a high fat diet — who both suffered from hyperglycemia — when Dentin and his colleagues decreased the activity of the hexosamine biosynthetic pathway in the liver of these animals.

"What I really would like to do is to use the glowing mice to screen for drugs that decrease gluconeogenesis," says Montminy. "Imagine hyperglycemic mice whose livers light up because CRTC2 is on all the time. When you feed them a drug that inhibits O-glycosylation the light dims and you know you have compound that's effective in living animals and you know how it works."

Source: Salk Institute