Blood sugar's manufacture limited by building blocks' supply

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Researchers have discovered a factor that controls blood sugar's manufacture in a novel way: by limiting the supply of its building blocks. The findings are reported in the April issue of the journal *Cell Metabolism*, published by Cell Press.

The study found that mice deficient for KLF15, a member of the so-called Krüppel-like family of transcription factors, become severely lacking in the blood sugar glucose—a primary energy source for the body and the sole source for the brain—after a period of overnight fasting. The researchers traced that deficiency back to an inability to produce new glucose in the liver, a process known as gluconeogenesis, due to a defect in the processing of amino acids. Amino acids are the main ingredients of proteins and the source of a key substrate in blood sugar's production.

"Gluconeogenesis is a complicated process," said Mukesh K. Jain of Case Western Reserve University. "It fundamentally requires two big things: the building blocks and the [glucose-building] enzymes that make it all happen. A lot of previous work has focused on the enzymes."

"We've found the first defect [in glucose production] due to a loss of substrate," added Susan Gray of Brigham and Women's Hospital.

During fasting, the supply of glucose derived from food dries up, Gray explained. In response, the body first breaks down liver glycogen, the principal storage form of glucose. However, the body "goes through

those stores overnight," she said.

Once the reserves are depleted, the body must rely on the synthesis of new glucose, primarily in the liver, to prevent a life-threatening shortage, a condition known as hypoglycemia. The de novo synthesis of glucose depends on the availability of a substrate molecule that comes from an amino acid.

The researchers found that mice with a targeted deletion of KLF15 display severe hypoglycemia after an overnight fast. They further found evidence that defective amino acid breakdown promotes the development of fasting hypoglycemia in the mutant animals by limiting the availability of a glucose substrate called pyruvate.

Indeed, the mice had markedly reduced activity of genes that encode amino acid-degrading enzymes, the researchers showed. The mice also had a deficiency in the activity of an enzyme that converts the critical amino acid, called alanine, into pyruvate. Consistent with this observation, injection of pyruvate, but not alanine, rescued the mice from their fasting hypoglycemia.

The findings point to a novel form of control over glucose levels, the researchers said. Ultimately, this "window into glucose control" might also have implications for diabetes treatment—a condition characterized by high glucose concentrations, Gray said.

"Inhibiting KLF15 might prove beneficial in people with type II diabetes who have too much glucose, partly because the liver produces more than necessary," Jain said.

"Their glucose sensor is off. If you attenuate KLF15 in the liver, you might limit glucose production."

Gray said she plans to further explore the underlying mechanisms involved in KLF15's glucose regulation and see how increasing KLF15 levels affects blood sugar production. Meanwhile, Jain plans to further examine the transcription factor's function in other parts of the body where it is active, namely in skeletal and heart muscle.

Source: Cell Press