MedicalXpress

Feast or famine: The switch that helps your liver adapt

August 25 2016

Scientists at the Sanford Burnham Prebys Medical Discovery Institute (SBP) have identified a previously unknown way that stress hormones (glucocorticoids) shut off genes in the liver to help the body adapt to the fasting state. The study, published today in *Cell Metabolism*, describes an obscure protein, SETDB2, that's increased during times of fasting and alters the genome to help turn on genes needed to adjust to the absence of food.

"Our study provides evidence that SETDB2 may be a potential therapeutic target to modulate glucocorticoid activity in metabolic diseases with altered glucocorticoid sensitivity such as obesity and diabetes, or in patients undergoing chronic glucocorticoid treatment," said Timothy Osborne, Ph.D., professor and director of the Integrative Metabolism Program at SBP, who directed the research. "These conditions are associated with liver dysfunction and can lead to nonalcoholic fatty liver disease (NAFLD) nonalcoholic steatohepatitis (NASH), fibrosis or liver cancer."

Glucocorticoids

Glucocorticoids are steroids secreted by the adrenal glands in response to stress signals from the brain. They help maintain normal concentrations of glucose in the blood and reduce inflammation, which can be beneficial in treating chronic autoimmune diseases and allergies.

"Synthetic glucocorticoids, such as prednisone, dexamethasone and

hydrocortisone have been prescribed for decades to stop inflammation. However, there are major side effects associated with steroid treatment, including immunosuppression that leaves a patient vulnerable to infection, and the exacerbation of metabolic diseases," added Osborne.

The yin and yang of metabolism

The new study, led by Manuel Roqueta-Rivera, a postdoctoral researcher in Osborne's lab, sought to find the mechanism that the liver uses to transition between the fed and fasted states—two extreme metabolic conditions that require genes to switch "on and off" to promote either energy storage or energy use.

Roqueta-Rivera induced a fasting state in mice by depriving them of food for 24 hours. In the liver, one of the genes activated by fasting was SETDB2, an enzyme that modifies other proteins, including histones—the proteins whose association with DNA helps control whether genes can be read.

Restoring metabolic equilibrium

"These results suggest that inhibiting SETDB2 could lessen certain metabolic side effects such as weight gain and insulin resistance in patients taking steroids for inflammatory disease," Osborne added. "Since SETDB2 only affects a subset of steroid hormone-regulated genes related to metabolism, we think this strategy would not interfere with steroids' anti-inflammatory effects.

"Modulating SETDB2 activity might also benefit patients with other metabolic conditions, but it's not clear yet whether it would be better to inhibit the enzyme or activate it. Blocking SETDB2 would likely lower blood glucose, which would be beneficial, but it might also enhance fat storage in the liver, which is damaging."

"Future therapies targeting SETDB2 likely wouldn't be one-size-fits-all," commented Osborne. "Metabolic disease is complex—its presentation varies widely—so if these drugs are developed, they could be targeted to specific patients."

Provided by Sanford-Burnham Prebys Medical Discovery Institute