

Inflammation linked with type 2 diabetes: Yale



How does insulin inhibit glucose production?

A Yale-led research team has identified the molecular mechanism by which insulin normally inhibits production of glucose by the liver and why this process stops working in patients with type 2 diabetes, leading to hyperglycemia.



“In the study, we set out to examine how insulin normally works to turn off production of glucose by the liver and why this process goes awry in patients with type 2 diabetes,” said Gerald I. Shulman, the George R. Cowgill professor of physiological chemistry, professor of medicine and cellular & molecular physiology at Yale School of Medicine, and an investigator with the Howard Hughes Medical Institute.

Experts have long debated how insulin suppresses glucose production by the liver. Many have asserted that insulin’s suppression of glucose production was due to the direct action of insulin on the liver. But the Yale-led team uncovered a different process that challenges current theories and may lead to new targets for treatment.

Yale researchers hypothesized that insulin suppressed glucose production by the liver by inhibiting the breakdown of fat,

which would result in a reduction in hepatic acetyl CoA, a key molecule that they showed was critical in regulating the conversion of amino acids and lactate to glucose. They also found that reversal of this process, due to inflammation in adipose (fatty) tissue, led to increased hepatic glucose production and hyperglycemia in high-fat-fed rodents and obese, insulin-resistant adolescents.

"These studies identify hepatic acetyl CoA as a key mediator of insulin action on the liver and link it to inflammation-induced hepatic insulin resistance and type 2 diabetes," Shulman explained.

This new insight into insulin resistance paves the way for exploring new treatments. "None of the drugs we currently use to treat type 2 diabetes target the root cause," said Shulman. "By understanding the molecular basis for hepatic insulin resistance we now can design better and more effective drugs for its treatment."

Reference:

"Hepatic Acetyl CoA Links Adipose Tissue Inflammation to Hepatic Insulin Resistance and Type 2 Diabetes," Gerald I. Shulman and colleagues, *Cell* Feb. 5, 2015 DOI 10.1016/j.cell.2015.01.012

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