Drugs that act on 'fasting signal' may curb insulin resistance in obese

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A report in the March issue of *Cell Metabolism*, a Cell Press publication, has found that a signal known to play a role during fasting also switches on early in the fat tissue of obese mice as they progress toward type 2 diabetes. Moreover, treatments that block that "fasting signal" in fat prevent the animals' resistance to insulin, according to the researchers.

While fasting and obesity may seem to have little in common, obesity actually resembles a fasted state, explained Marc Montminy of the Salk Institute for Biological Studies. In obesity, the shift from glucose to fat burning that usually takes place only when the body is fasted continues around the clock.

"That excessive fat goes to places it shouldn't go, including liver and muscle," he said. "The free fatty acids accumulate and muck up the works."

Earlier studies had shown that the so-called CREB family of transcription factors mediate the effects of chemicals that increase the breakdown of fat stores as well as other fasting hormones. For instance, CREB keeps blood sugar in balance during fasting by triggering the production of glucose in the liver. Excessive activity of CREB in diabetes contributes to high blood sugar and insulin resistance, according to earlier reports. Studies had also suggested CREB might play a role in fat cell precursors.

In the new study, the researchers wanted to find out whether the pathway

was important in mature fat tissue as well. And indeed it is. CREB is active in fat cells under obese conditions, where it encourages insulin resistance by lowering the production of a hormone called adiponectin as well as the insulin-sensitive glucose transporter 4 (GLUT4), they report.

Genetically altered mice that lack CREB in fat cells become more sensitive to insulin both in the contexts of diet-induced and genetic obesity, the researchers found. Obese animals deficient for the CREB signal were also protected from the development of fatty liver and inflammation in fat tissue.

The surprising thing, Montminy said, was that CREB seemed to be relatively unimportant in healthy animals fed normal mouse chow. In obese animals the signal seems to be "doing something more pathological. It suggests the stress of obesity activates CREB genes and contributes to insulin resistance."

The discovery may have clinical implications.

"Taken together, these results show that targeting therapies to adipose tissue and, in particular, to the CREB signaling system could have important therapeutic benefits in a variety of insulin-resistant states," the researchers concluded.

Nevertheless, Montminy added, treatments that target CREB itself may not be the answer. That's because CREB is involved in other parts of the body, including the brain where it has a role in memory. He suspects that therapies designed to hit proteins that coactivate CREB might more specifically target its activity in particular tissues. That's a notion he says his team is now exploring in greater detail.

Source: Cell Press

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