UCSD Study Sheds New Light on Insulin's Role in Blocking Fat Breakdown in Patients with Type II Diabetes

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Chronically high levels of insulin, as is found in many people with obesity and Type II diabetes, may block specific hormones that trigger energy release into the body, according to researchers at the University of California, San Diego (UCSD) School of Medicine. Their findings, which may point to new approaches to developing improved treatment options for the disease, will be published in the September 22 issue of the journal Nature.

The research team, led by Roger Y. Tsien, professor in UCSD's Departments of Pharmacology and Chemistry and Biochemistry and a Howard Hughes Medical Institute investigator, found that high levels of insulin can block stress hormones known as catecholamines, which normally cause the release of cellular energy. Adrenaline is the best known example of a catecholamine. For normal metabolism to occur, the body needs a balanced input of insulin and catecholamines. One of the actions of insulin --, the main energy storage hormone, is to block activation of the protein kinase A (PKA) enzyme. After a meal, insulin levels go up, and the body stores energy primarily as triglycerides, or fat, in adipose tissue to be used later. When energy is needed, catecholamine triggers activation of PKA, and energy is released. But in people with Type II diabetes, the hormonal balance has been thrown off, because the body continues to produce and store more triglyceride instead of breaking down the fat as released energy.

"Somehow, insulin knows how to specifically block catecholamine-induced PKA, but not other molecules," said Christopher Hupfeld, assistant professor of Medicine in the UCSD Division of Endocrinology and Metabolism and a co-author of the paper. "When the body has a constantly high level of insulin, this energy- release stimulus is lost."

The team's findings provide new understanding to the cause and effect occurring when insulin levels are too high. It also underscores the goal of physicians to bring down insulin levels in Type II diabetes using medicines called insulin sensitizers, so that the body becomes more sensitive to using its own insulin, rather than compensating for insulin resistance by making more.

In order to understand the mechanisms of insulin resistance present in Type II diabetes, the researchers used a new breed of cellular enzyme reporter to track PKA. The reporter is a "marker" protein, created with special fluorescent tags so that scientists can physically view the protein under a microscope and watch how the live cell activates PKA in real time.

The PKA is normally activated inside the adipocyte cell, the major site of energy storage in the body where many aspects of metabolism are controlled. There, energy is stored in the form of triglycerides, commonly known as fat. If a person is obese, excess triglycerides are stored in the adipocytes. The new study shows that insulin weakens the normal linkage between catecholamine receptors and the turn-on of PKA.

"If insulin levels get too high for too long a time - which happens in many patients with type II diabetes -the normal catecholamine signal that triggers fat breakdown and energy release can be drowned out. This can lead to excessive energy storage in the adipocyte," said Hupfeld. "This may be one reason why chronic obesity and Type II diabetes are often seen together."

"By correcting this hormonal imbalance, researchers may at some point improve treatment options for both obesity and Type II diabetes," said Hupfeld.

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