Team illuminates cell pathway key to insulin resistance in type 2 diabetes

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A research team, led by La Jolla Institute scientist Joel Linden, Ph.D., has shed new light on the problem of insulin resistance, and identified the key participants in a molecular pathway that holds therapeutic promise for reducing the severity of type 2 diabetes.

The researchers looked at the role of adenosine, an immune system signaling molecule, in triggering inflammation, which significantly contributes to insulin resistance. Insulin resistance keeps the body from properly handling sugar and is one of the key factors underlying type 2 diabetes. Diabetes now affects nearly 26 million Americans and is the seventh leading cause of death in the U.S., according to the Centers for Disease Control.

"Several previous studies have shown that if you block adenosine signaling, insulin resistance is diminished," said Dr. Linden. "However, it wasn't known exactly how the process worked or which cells were directly involved."

Dr. Linden's team identified the primary cellular players in the adenosine-fueled inflammation cascade that contributes to insulin resistance. Their study, in animal models, also tested the effectiveness of a recently synthesized adenosine receptor blocker. "We found that if you use this molecule to selectively block one of the adenosine receptors, insulin resistance is decreased and diabetes gets better," said Dr. Linden, one of the world's leading authorities on adenosine.

Eugene Barrett, Ph.D., a past president of the American Diabetes Association, praised the study's findings as important. "There is a great need for new approaches to lessen the disease burden caused by insulin resistance," said Dr. Barrett, a professor of medicine and director of the University of Virginia's Diabetes Center, which was not involved in the study. "The work of Dr. Linden and his collaborators opens a new avenue to explore with possibly important therapeutic implications."

The findings were published in a paper entitled "Links Between Insulin Resistance, Adenosine A2B Receptors, and Inflammatory Markers in Mice and Humans" in the February issue of the scientific journal *Diabetes*. Dr. Linden was senior author on the study, which involved scientists from Pennsylvania State University, the University of Virginia, the La Jolla Institute for Allergy & Immunology and Clinical Data, Inc., a pharmaceutical company examining possible therapeutic applications targeting adenosine receptors. Robert A. Figler, Ph.D., of Clinical Data Inc. was first author on the paper.

"Our study clarifies the molecular steps triggered by adenosine, which leads to inflammation linked not only to type 2 diabetes but to other inflammatory diseases," Dr. Figler said. Clinical Data has an ongoing development program in A2B receptor antagonists, he added, and is pursuing the therapeutic potential of these agents in diabetes as well as asthma. Clinical Data plans to soon begin a clinical trial for patients with asthma.

In type 2 diabetes, Dr. Linden explained, the ability of insulin to stimulate glucose uptake by the tissues is reduced, an occurrence known as insulin resistance. "Insulin's job is to move glucose out of the blood stream and into other body tissues, where it can be used," he said. "If insulin can't do its job because the body's tissues aren't responding to it sufficiently, then you end up with a buildup of sugar in the blood."

"So we asked ourselves the question," Dr. Linden continued, 'why don't the tissues respond?'"

Recently, said Dr. Linden, the scientific community has learned that type 2 diabetes is associated with chronic low-grade inflammation. "We believe, as do many scientists, that insulin resistance involves macrophages, which are cells of the body that contribute to inflammation," he explained. "We discovered that adenosine stimulates macrophages. The macrophages then release chemicals called cytokines, which are molecules that rev up the immune system. We believe it is the cytokines that cause tissues to become less sensitive to insulin."

By using an adenosine receptor blocker, the team prevented the adenosine from activating the macrophages, said Dr. Linden. "So the downstream effect of releasing cytokines does not occur." The result? The tissues began to better respond to insulin, which reduces blood sugar levels in diabetic animals.

While sensitivity to insulin was significantly improved, Dr. Linden said insulin resistance was not completely reversed. "We will be studying this further to better understand the details of insulin resistance," he said.

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