ScienceDaily
Your source for the latest research news

Source: **University Of California - San Diego** ***Date:*** **February 3, 2005**

Pro-inflammatory Enzyme Linked To Diabetes; Immune System's Macrophages May Be Key To Treatment

Science Daily — An enzyme that initiates inflammation has been directly linked to insulin resistance and resulting type II diabetes by researchers at the UCSD School of Medicine. In addition, the team suggests that inhibition of the enzyme in the immune system's macrophages may be a new diabetes therapy.

Both control mice and mice with Ikk-ß deleted in specific types of cells were fed a high-fat diet that normally causes metabolic syndrome and type II diabetes. While the control mice developed the diabetes and insulin-resistant symptoms, mice in which the Ikk-ß was deleted from microphages retained their healthy insulin levels.

"The potential for a new diabetes treatment is great," said one of the study's senior authors, Jerrold Olefsky, M.D., chief of UCSD's Division of Endocrinology and Metabolism in the Department of Medicine, and associate dean for scientific affairs for the School of Medicine. "An inhibitor of Ikk-ß could be used, or an inhibitor of any other molecule in the inflammation pathway."

Affecting 18.2 million Americans, diabetes is a disease in which the body does not produce or properly use insulin, a hormone necessary to convert sugar, starches and other food into energy needed for daily life. Previous studies in the past few years have implicated inflammation as playing a role in diabetes, but just how this occurred was unknown.

The researchers generated mice without Ikk-ß in liver cells that play a direct role in insulin-regulated glucose metabolism, and in systemic myeloid cells, pivotal players in inflammatory responses as they produce macrophages.

In response to challenges with a high-fat diet, mice with Ikk-ß deficient myeloid cells retained insulin sensitivity in all target tissues. Because the myeloid cells (and their macrophages) are systemic able to travel throughout the body they were identified by the researchers as the best target for diabetes treatments.

The mice lacking Ikk-ß only in the liver retained their insulin sensitivity in the liver but became insulin resistant in fat and muscle. Other tissue, such as muscle, was not tested in this study, because a previous study has shown that deletion of Ikk-ß in muscle has no effect on obesity-induced insulin resistance and type II diabetes, although muscle is a major insulin-responsive tissue.

In addition to Olefsky, a senior author of the paper was Michael Karin, Ph.D., UCSD professor of pharmacology, an American Cancer Society Research Professor, and the scientist who first discovered IKK and its subunits. The paper was a collaborative effort between the diabetes lab of Olefsky and Karin's molecular signaling lab in the department of pharmacology.

Additional authors included first author Melek C. Arkan, UCSD Department of Pharmacology; and Andrea L. Hevener, UCSD Division of Endocrinology and Metabolism, Department of Medicine; Florian R. Freten, Shin Maeda, Zhi-Wei Li, UCSD Division of Endocrinology and Metabolism, Department of Medicine; Jeffrey M. Long, Ph.D., and Anthony Wynshaw-Boris, M.D., Ph.D., UCSD Departments of Pediatrics and Medicine; and Giuseppe Poli, S. Luigi Hospital, University of Turin, Italy. The study was funded by the National Institutes of Health.

Note: This story has been adapted from a news release issued by University Of California - San Diego