Endocannabinoids trigger inflammation that leads to diabetes

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(Medical Xpress)—Researchers at the National Institutes of Health have clarified in rodent and test tube experiments the role that inflammation plays in type 2 diabetes, and revealed a possible molecular target for treating the disease. The researchers say some natural messenger chemicals in the body are involved in an inflammatory chain that can kill cells in the pancreas, which produces insulin.

A report of the finding appears online in *Nature Medicine*.

"This study is a significant milestone in an ongoing exploration of the endocannabinoid system's role in the metabolic complications of obesity ," says Kenneth R. Warren, Ph.D., acting director of NIH's National Institute on Alcohol Abuse and Alcoholism (NIAAA), which led the study.

Endocannabinoids are natural messengers in the body that help regulate many biological functions. They are chemically similar to the active compound in marijuana. Recent studies have tied endocannabinoids to the metabolic problems that lead to diabetes. Researchers also have recognized that inflammation appears to play an important role in the pathology of diabetes.

"The identities of the molecular and cellular actors in the inflammatory processes that underlie type 2 diabetes have remained elusive," explains senior author and NIAAA scientific director George Kunos, M.D., Ph.D. "Our study connects endocannabinoids to an inflammatory cascade

leading to the loss of beta cells in the pancreas, which is a hallmark of type 2 diabetes."

Working with a strain of genetically obese rats that serve as a model for human type 2 diabetes, Dr. Kunos and his colleagues used a combination of pharmacological and genetic tools to show that endocannabinoids trigger receptors on macrophages in the pancreas. Macrophages are immune system cells, present in all tissues that rid the body of cellular debris and pathogens.

"Like various other peripheral tissues, such as the liver, skeletal muscles, pancreas, and fatty tissue, macrophages have receptors for endocannabinoids," explains Dr. Kunos.

The researchers demonstrated that endocannabinoid activation of macrophages in the pancreas leads to activation of a protein complex within macrophages called the Nlrp3 inflammasome. The inflammasome, in turn, releases molecules that cause the death of pancreatic beta cells and the progression of type 2 diabetes in the rats.

"When we treated the rats with compounds that deplete macrophages or block all peripheral cannabinoid receptors, inflammasome activation and type 2 diabetes progression was slowed," noted Dr. Kunos.

In test tube experiments, the researchers showed that macrophages from humans and mice produced the same inflammasome response when they were incubated with endocannabinoids. However, mouse macrophages that were genetically altered to lack cannabinoid receptors or inflammasomes generated no such response.

Most notably, the researchers showed that by selectively blocking the expression of cannabinoid receptors on macrophages, they could protect and restore beta cell function in the genetically obese rats, which delayed

the development and reduced the severity of their diabetes.

The authors conclude that the findings point to a key role in type 2 diabetes for endocannabinoid-induced inflammasome activation in macrophages, and identify cannabinoid receptors on macrophages as a new therapeutic target.

"To understand type 2 diabetes, a public health threat that affects young and old alike, we need to consider all the factors at play," said Monica Skarulis, M.D., staff clinician at National Institute of Diabetes and Digestive and Kidney Diseases and co-author. "We hope that what we've learned from this research will help us develop new strategies to prevent and treat the condition."

More information: Jourdan, T, et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. *Nature Medicine*, 2013 August 18.

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