Mouse study offers clues to obesity-diabetes link

December 6 2012, by Lisa Esposito, Healthday Reporter

Researchers hope to cut the connection between fatty diet and insulin resistance, but it's complicated.

(HealthDay)—Obesity and type 2 diabetes are clearly intertwined, but researchers say they've found a way to weaken the connection between the two—at least in mice.

The key, they say, is blocking the body's inflammation response to high-fat foods.

In this study, published online Dec. 6 in the journal *Science*, the researchers turned off the JNK (pronounced "junk") genetic pathway in mice, and fed the rodents high-fat diets. Even though the mice became obese, they didn't develop insulin resistance, a forerunner to diabetes.

Other similarly stuffed mice with intact JNK pathways, however, became insulin resistant.

Although the results look promising, it's too early to say whether the findings might apply to humans.

"Everybody has these genes, and they're present within all cells of your body all the time," said study author Roger Davis. "What they do is respond to the diet that you're eating. So if you eat a high-fat, cafeteria diet, it leads to the activation of the protein products—the enzymes—of these genes."

Davis, a professor at the University of Massachusetts Medical School and investigator at the Howard Hughes Medical Institute in Worcester, Mass., and his colleagues studied hundreds of mice over multiple years to examine the relationship between inflammation and diabetes.

"What we discovered is the JNK genes in the macrophages are critical for the ability of macrophages to cause inflammation, specifically in response to feeding or eating a high-fat diet," Davis said.

Macrophages—white blood cells—attack foreign invaders of the body. They fight infection but their inflammatory response can be harmful too. Inflammation has been linked to conditions such as arthritis, heart disease and cancer.

In the study, mice, "by not having the JNK genes in the macrophages, it prevents the inflammation that takes place in the body in response to feeding and diet, and that in turn prevents the development of symptoms of prediabetes, like insulin resistance," Davis said.

Dr. Joel Zonszein, director of the Clinical Diabetes Center at Montefiore Medical Center in New York City, who was not associated with the study, said science in this area has gone beyond realizing that having more body fat—particularly more "central" or waistline body fat—is a risk factor for diabetes.

"We have the so-called healthy obese who have less fatty tissue, they have less inflammation, they have less macrophages," Zonszein said. "And we have some people who don't look very obese but their [fat] tissue is loaded with macrophages, particularly bad macrophages."

The new mouse study, Zonszein said, "is one unique pathway that they identified in a very nice way—because we always have associated obesity with insulin resistance, but in their model [the mice] develop obesity but their insulin's healthy."

Zonszein added, however, that what goes on in the human body is much more complex. "Nonetheless, this is science—something that we need to learn from. But from this to drug-development implications in humans, there is a big, big stretch," he said.

Study author Davis acknowledged the gap between animal research findings and clinical benefits, but said it might be bridged.

"One possible scenario—and obviously our work is on mice, so there's a big leap of faith here to establish [this] in humans—but the work we've done would suggest that drugs that are targeted to JNK kinase genes would be useful for the treatment of diabetes," he said. "But this is definitely a big step beyond the point of our own work."

One take-away message, Davis said, is that eating unhealthy foods immediately affects your body.

"It's useful for people to recognize that the foods they eat have these very direct biochemical effects," he said. "Sometimes people think that you eat a poor diet and at some later time there are some bad effects that secondarily occur. But some of these things can be much more direct."

More information: "JNK Expression by Macrophages Promotes

Obesity-Induced Insulin Resistance and Inflammation," by M.S. Han, *Science*, 2012.

The U.S. National Library of Medicine has more about dietary fat.