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Researchers uncover 'obesity gene' involved in weight gain response to high-fat diet

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Scientists have determined that a specific gene plays a role in the weight-gain response to a high-fat diet. The finding in an animal study suggests that blocking this gene could one day be a therapeutic strategy to reduce diet-related obesity and associated disorders, such as diabetes and liver damage, in humans.

The researchers found that a diet rich in fat induced production of this gene, called protein kinase C beta (PKC beta), in the fat cells of mice. These mice rapidly gained weight while eating a high-fat diet for 12 weeks.

On the other hand, mice genetically engineered to lack PKC beta gained relatively little weight and showed minimal health effects after eating the same high-fat diet.

In comparing the effects of the high-fat diet and a regular diet, the scientists found that mice fed the high-fat diet produced more PKC beta in their fat tissue than did mice eating a regular diet.

"So we now know this gene is induced by a high-fat diet in fat cells, and a deficiency of this gene leads to resistance to fat-induced obesity and related insulin resistance and liver damage," said Kamal Mehta, senior author of the study and a professor of molecular and cellular biochemistry in Ohio State University's College of Medicine.

"It could be that the high-fat diet is a signal to the body to store more fat.

And when that gene is not there, then the fat storage cannot occur."

Though the complete mechanism remains unknown, the research to date suggests that rather than storing fat, mice lacking the gene burn fat more rapidly than they would if the PKC beta were present, Mehta said.

The research is available online in the journal *Hepatology* and is scheduled for later print publication.

Mehta and colleagues previously had created the hybrid mouse model by cross-breeding mice deficient in PKC beta with the C57 black mouse, a common animal used in research for studying diabetes and obesity. Despite the propensity for obesity from their original genes, the new mice lost weight while eating up to 30 percent more food than other mice.

In the earlier study, the mice ate a regular diet. In this new study, the researchers fed PKC beta-deficient and normal mice either a diet in which 60 percent of calories were derived from fat - the high-fat diet - or a standard diet in which 15 percent of calories came from fat. In the typical American diet, about 40 percent of calories are derived from fat.

The normal mice on the high-fat diet showed weight gain within three weeks, a trend that continued throughout the 12-week study. The PKC beta-deficient mice on the same diet gained less weight even while appearing to be extra hungry and eating more calories than the normal mice - meaning their lower body weight was not the result of eating less.

Of animals eating the high-fat diet, the fat tissue and livers in the normal mice were larger than those in the PKC beta-deficient mice, as well. The livers of the normal mice were on average about 50 percent larger than the livers in mice lacking the gene. And the white fat tissue - the tissue in which PKC beta was expressed as a result of the high-fat diet - was

almost three times as heavy in the normal mice as in the PKC beta-deficient mice.

The protein-deficient mice were able to clear insulin to regulate blood sugar more rapidly than normal mice after eating the high-fat diet, meaning avoiding obesity also allowed them to avoid development of insulin resistance associated with diabetes, said Mehta, also an investigator in Ohio State's Davis Heart and Lung Research Institute.

"Obesity leads to liver damage and to diabetes. So if we can take care of obesity associated with a high-fat diet, we can also take care of most of the related disorders," Mehta said.

A separate component of the current study further showed that mice engineered to be obese also had about 500 percent more of the gene in their fat cells than did normal mice. Mehta and colleagues have assembled a team that includes an endocrinologist, bariatric surgeon and molecular biologist to examine human fat tissue from obese and lean patients to see if levels of PKC beta are elevated in obese humans, as well.

"It is very likely that this gene may be involved in a predisposition to obesity," he said.

Knowing the gene is responsive in the fat cells is important to figuring out how to suppress its action. Future research will involve deleting the gene from fat cells in mice to see if these new mice have the same lean body type as mice that are completely deficient of PKC beta throughout their entire genome.

"We are generating more mouse models to vary expression of this gene and study the consequences of that on obesity and related disorders," Mehta said.

So far, mouse models lacking the protein have not shown any damaging side effects related to the suppression of the gene, Mehta said. He speculates that PKC beta could be a so-called "thrifty" gene left over from humans' days as hunter-gatherers, when the body needed to retain fat for survival.

Source: Ohio State University

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