Protein deficiency leads to faster fat burning in mice, study shows

March 12 2008

Researchers have developed a new, lean mouse with characteristics suggesting that someday, using medication to manipulate a specific protein in humans could emerge as a strategy to treat obesity and disorders associated with excess weight, such as diabetes and metabolic syndrome.

To create the hybrid, scientists crossed mice deficient in protein kinase C beta (PKCB) with the C57 black mouse, a common animal used in research for studying diabetes and obesity.

“These animals can eat more than normal. And they have less fat than normal. That’s a dream come true if it can be extended to human beings,” said Kamal Mehta, senior author of the study and a professor of molecular and cellular biochemistry at Ohio State University.

He noted, however, that an appropriate therapy for humans would take years to develop.

At first glance, compared to mice with no deficiency, these new hybrid mice were smaller and leaner. And when the researchers looked under their skin, they saw the mice had less fat distribution in the skin itself and less fat tissue overall. They also had less fat in their livers and muscles. The fat cells they did have were smaller than fat cells in other mice.

And 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. This means their lower weight was not caused by less eating, suggesting the protein deficiency corrected for the obesity tendencies by increasing the hybrids' ability to burn fat, said Mehta, an investigator in Ohio State's Davis Heart and Lung Research Institute.

The research is published in a recent issue of the *Journal of Biological Chemistry*.

Based on his previous research on the role of PKCB in metabolism, Mehta expected a deficiency of the protein to affect how the body processes triglycerides, or fat stored in body tissue.

"The bottom line is we were the first to show that this deficiency leads to a lean animal. The next question is why," Mehta said. "In order to answer why, we need to know which genes are changed in these knockout animals."

The most prominent effect the scientists have been able to identify so far relates to the mitochondria, the principal energy source of cells. Mehta said the new hybrid mice have more mitochondria within their cells than do normal mice, and that the added energy source allows them to convert fatty acids into energy.

"We have shown to some extent that there is increased fatty acid oxidation. We found that they use more oxygen, so that means they are using this oxygen to metabolize fat, convert it into carbon dioxide and expel it when they breathe," said Madhu Mehta, a clinical consultant and co-author on the study and assistant professor of internal medicine at Ohio State.

The research group is testing this finding with an additional experiment, introducing the PKCB deficiency to animals with a lower production of

mitochondria to see if the level of mitochondria increases when the protein is not present.

More work also needs to be done to determine whether the protein could be deficient in just certain types of cells to produce the same effect – for example, by eliminating the protein from only liver cells or fat tissue cells rather than throughout the body. Under current circumstances, the deficiency is present in the entire mouse genome.

“So we need to find which specific tissue needs the deficiency. Once we know which tissue is crucial for this, we can target that,” Kamal Mehta said. “The whole idea is to be able to develop a drug that would safely create this deficiency in humans.”

Mehta also is leading a study testing the effect of PKCB deficiency on diabetes in particular, examining whether the disease can be prevented by the elimination of this protein. An excess of triglycerides in tissue can lead to insulin resistance, a hallmark of diabetes. Because the protein relates to how the body burns triglycerides, Mehta believes the deficiency also could play a role in preventing the disease from developing.

The deficiency does not appear to pose any health problems. The mice with the deficiency lived a normal lifespan and experienced no premature deaths.

It remains unknown whether the deficiency currently exists naturally in humans. “Genetic testing of lean people could help answer that question,” Mehta said.

Source: Ohio State University