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## **Monell researchers find metabolic defect in liver that can lead to obesity**

*Study opens door to development of new obesity drugs*

Philadelphia (July 24, 2007) -- Researchers at the Monell Chemical Senses Center have identified a genetically-transmitted metabolic defect that can lead to obesity in some individuals. The defect involves decreased production of liver enzymes needed to burn fat and may help to explain why some people become obese while others remain thin.

The global obesity epidemic is thought to be caused in part by the increased availability and intake of high calorie foods rich in fat and carbohydrates. These foods promote weight gain in humans and other animals, leading to a diet-induced obesity. The propensity to gain weight and become obese when consuming a high-fat diet is at least partially controlled by genes.

“Results of this study help explain the interaction between genes and diet that underlies diet-induced obesity,” comments senior author Mark Friedman. “They also point to a way to identify individuals at risk for dietary obesity, perhaps even during childhood before the development of unhealthy eating habits.”

The current study, published in the August issue of *Metabolism*, demonstrates that genetic susceptibility to diet-induced obesity is due to a reduced capacity to burn fat.

Fat is one of the fuels that the body's cells burn to provide energy. This process, known as fat oxidation, takes place inside mitochondria, the cell's power plants for generating energy.

If the ability to oxidize fat is impaired, the body's capacity to make energy is reduced. This leads to increased hunger and overeating, as the body tries to increase the amount of energy available to meet its needs.

When the diet is low in fat, a reduced ability to burn fat has relatively little impact on energy production. However, if fat oxidation is impaired and the diet is high in fat, a greater proportion of calories cannot be used and food intake increases to cover the energy deficit. Because fat fuels are stored in fat tissue when they're not oxidized, the increased food intake causes weight gain.

To determine whether preexisting differences in fat oxidation might contribute to individual susceptibility to diet-induced obesity, Friedman and lead author Hong Ji used rats that differ in their genetic predisposition to gain weight and become obese when fed a high-fat diet.

The closely-related strains weigh the same and eat the same amount of calories when fed a low-fat diet. However, when switched to a high-fat diet, the strain that is obesity-prone overeats and becomes obese, while the obesity-resistant strain does not.

The researchers found that even when eating a low-fat diet and still lean, the obesity-prone rats were less able to burn fat than were the obesity-resistant rats. This intrinsic deficit in fat oxidation was associated with a decrease in the capacity to make two liver enzymes. One, CD36, is responsible for transferring fat fuels into liver cells, while the second enzyme, acyl-coenzyme A dehydrogenase, begins the oxidation process in mitochondria.

When fed a high-fat diet, the obesity-prone rats overate and became obese, gaining 36% more weight than resistant animals. Fat oxidation was further compromised due to a decreased ability to make CPT1A, the liver enzyme responsible for transporting fat into mitochondria.

“The inherited propensity to gain weight when eating a high-fat diet appears to be due to a preexisting limit on the ability to burn fat in the liver. This defect persists during the development of obesity and is then further compounded by additional deficits in the fat oxidizing machinery,” comments Friedman.

Other studies in Friedman’s laboratory have demonstrated that a decrease in fat oxidation and energy production in the liver generates a signal that stimulates eating. Experiments in his and other laboratories have also found that treatments that increase fat oxidation reduce food intake and cause weight loss in obese rodents.

With this in mind, Friedman notes, “The present findings point to fat oxidation in the liver as a target for the development of drugs that suppress appetite and promote weight loss in obese individuals.”

Future studies will guide development of such interventions by examining more closely the function and activity of the target enzymes.

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The Monell Chemical Senses Center is a nonprofit basic research institute based in Philadelphia, Pennsylvania. For 39 years, Monell has been the nation’s leading research center focused on understanding the senses of smell, taste and

chemical irritation: how they function and affect lives from before birth through old age. Using a multidisciplinary approach, scientists collaborate in the areas of: sensation and perception, neuroscience and molecular biology, environmental and occupational health, nutrition and appetite, health and well being, and chemical ecology and communication. For more information about Monell, please visit [www.monell.org](http://www.monell.org).

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