Diet, Metabolism and Obesity

Mark I. Friedman
Monell Chemical Senses Center

January 7, 2009

Introduction

Obesity is a rapidly growing worldwide public health problem, and overconsumption of energy-dense foods rich in fat is considered an important contributing cause. The etiology of such diet-induced obesity remains unclear, but appears to involve inherited components that make some individuals susceptible to this form of obesity. Whereas the consequences of dietary obesity have been well characterized, little is known about the nature of the diets and genetic factors that interact to cause excess weight gain. Such knowledge will be critical for the prevention and treatment of obesity and research performed at Monell is contributing to our understanding of the genetic and dietary causes of this condition.

Diet Composition and Obesity

Even though nutritional factors are known to be important, there have been relatively few studies to establish what features of the diet contribute to the development of obesity. Instead, it is generally assumed that dietary fat is the culprit; however, studies in laboratory animals and humans show that this is only part of the story. The complete story involves an interaction between dietary fat and carbohydrate. Previous and ongoing studies at Monell have shown that if rats are fed a diet high in fat, but low in carbohydrate, they do not overeat and become obese. Only when the diet contains substantial amounts of both fat and carbohydrate dot rats overeat and develop obesity. The effectiveness of Atkins-type diets, which are high in fat and low in carbohydrate is consistent with this finding. Such a diet fosters weight loss with less hunger than does one low in fat and rich in carbohydrates.

Genetic Markers for Obesity

Not all humans nor all laboratory rodents become obese eating a carbohydrate-rich, high-fat diet. Some individuals are prone to such diet-induced obesity and others are resistant, a difference that is based on genetic factors. Except for those rare instances in which obesity can be attributed to a single gene mutation, there has been little success identifying gene mutations that cause obesity. Indeed, as shown by an analysis by Monell scientists the large number of genes that have been associated with changes in body weight suggests that a single gene for obesity does not account for the excess weight gain or the degree of risk for obesity.

Fat Metabolism and Obesity

Compared to genetic markers, pre-existing differences in fat metabolism have been better at distinguishing between rats that will become obese after eating a high-fat, high-carbohydrate diet and those that do not. Monell scientists have shown that fasting plasma triglyceride levels or the change in plasma triglycerides after a fat meal are highly predictive of weight gain in rats after they are switched from a low-fat diet to a diet rich in carbohydrates and fat. The relationship between blood triglyceride level and the propensity to gain weight may be tied to the capacity to oxidize (burn) fat because i*n vivo* fat oxidation is lower in rats that subsequently become obese after eating a carbohydrate-rich, high-fat diet than it is in rats that do not become obese. Furthermore, this relationship is not just seen in rats: Low rates of fat oxidation are also predictive of subsequent weight gain in humans and previously obese women oxidize less of a fat meal than do lean women.

Reduced Ability to Burn Fat Leads to Obesity

Research at Monell indicates that it is a reduced capacity to burn fat specifically in the liver that may drive dietary obesity. Ketone bodies are products of fat oxidation in liver and rise during fasting. Thus, the finding that fasting plasma ketone body levels in rats prone to dietary obesity are only 50% that obesity-resistant rats strongly suggests a deficit in hepatic fat oxidation. This is also consistent with the observation that oxidation of fat in hepatocytes (liver cells) isolated from rats identified as obesity-prone using the blood triglyceride tests described above is half that in hepatocytes from rats identified as obesity-resistant. The expression of proteins in liver (but not muscle) that are crucial to the ability to burn fat are also lower in obesity-prone rats. Finally, administration of a drug that stimulates fat oxidation in the liver reverses diet-induced overeating and obesity at a dose that does not affect food intake or body weight in rats that are resistant to dietary obesity.

Importance of Identifying Those at Risk for Obesity

The ability to predict who is a most risk for developing obesity or regaining weight after successful dieting would be an important step forward in the prevention and treatment of obesity. If precious resources could be focused on those most at risk it would increase the chances for success in the most efficient manner. Although the above findings are promising, additional work in animals and people is sorely needed. Future research at Monell will be done to improve the power of blood lipids to predict weight gain. This will likely involve further experiments in rats, but eventually the value of such biomarkers in humans must be evaluated. Similarly, other studies at Monell are planned to develop measures of fat oxidation that are simple and fast are needed to determine the utility of this parameter as a biomarker for obesity. The development of noninvasive measures, such as a breath test, would be particularly valuable if these biomarkers are to be used in the clinic and especially with children. Studies designed to test and refine the use of metabolic biomarkers for obesity, would have additional benefit of providing insight into the mechanisms of dietary obesity. This in turn might lead to the

identification of new targets for the treatment of obesity and would inform the evaluation of potential dietary and pharmaceutical remedies.

Selected references:

Ramirez, I. and M.I. Friedman. Dietary hyperphagia in rats: role of fat, carbohydrate and energy content. Physiology & Behavior, 47: 1157-1163, 1990.

Ji, H. and M.I. Friedman. Fasting plasma triglyceride levels and fat oxidation predict dietary obesity in rats. Physiology & Behavior, 78: 767-772, 2003.

Ji, H. and M.I. Friedman. Reduced capacity for fatty acid oxidation in rats with inherited susceptibility to diet-induced obesity. Metabolism, 56: 1124-1130, 2007.

Ji, H. and M.I. Friedman. Reduced hepatocyte fatty acid oxidation in outbred rats pre-screened for susceptibility to diet-induced obesity. International Journal of Obesity, 32: 1331-1334, 2008.