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EDITORIAL

Putting your genes on a diet: the molecular effects of carbohydrate[1,2,3]

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Traditionally, food is thought to influence human health through its nutrient content, whereas drugs are recognized to act through molecular pathways. However, consumption of a meal stimulates the release of numerous hormones that can powerfully affect signal transduction and gene function. The article by Kallio et al (1) in this issue of the Journal highlights this possibility by demonstrating changes in gene expression in individuals consuming diets with different effects on postprandial insulin concentrations.

The authors randomly assigned adults with features of the metabolic syndrome to a rye-pasta (low insulin response) or an oat-wheat-potato (high insulin response) diet for 12 wk. The diets were designed to be similar in energy, fiber, and macronutrient contents, although modest differences in fiber, carbohydrate, and protein contents were documented by food records. Gene expression in subcutaneous fat was evaluated at baseline and at 12 wk with microarrays and quantitative polymerase chain reaction. In individuals in the low-insulin-response group, 71 genes showed decreased expression and none showed increased expression. Of particular interest, several down-regulated genes have links to insulin-signaling pathways and apoptosis. In contrast, in individuals in the high-insulin-response group, 62 genes showed increased expression and none showed decreased expression.

Prior microarray studies found differences in gene expression between overweight and lean individuals (2) and after energy restriction (3); however, changes in the ratio of fat to carbohydrate did not alter gene expression (3). The study by Kallio et al makes a significant contribution to the literature by demonstrating the potentially major effects of dietary composition on gene regulation, independent of energy intake and body weight. Two specific findings concerning the low-insulin-response diet merit particular attention: the down-regulation of both hormone-sensitive lipase (HSL) and TCF7L2.

HSL, a key enzyme in the release of fatty acids from adipose tissue, has been proposed to affect body weight and metabolic variables. Mice made deficient in HSL by genetic manipulation are resistant to genetic- or diet-induced obesity (4, 5). Women carrying an allele associated with decreased HSL activity have lower fasting and simulated insulin concentrations, and men with this allele have lower nonesterified fatty acid concentrations (6). In light of these data, proteins involved in lipolysis have become targets of drug development for the treatment of obesity and

the metabolic syndrome. Thus, decreased HSL activity might mediate some of the purported benefits of diets designed to lower insulin secretion.

The transcription factor TCF7L2 is the strongest known genetic predictor of type 2 diabetes. A microsatellite within intron 3 of this transcription factor occurs with increased frequency in individuals with type 2 diabetes, which corresponds to an estimated population attributable risk of 21% (7). Although the mechanisms involved in disease risk have not been fully elucidated, TCF7L2 affects the Wnt signaling pathway and may be critical for glucagon-like peptide 1 (GLP-1) secretion by intestinal endocrine L cells. Decreased secretion of GLP-1 appears to play a role in the development of type 2 diabetes, and GLP-1 agonists have recently been developed for the treatment of diabetes.

The present study has direct implications concerning our understanding of the dietary glycemic index (GI). The GI is a system for classifying carbohydrate-containing foods according to how blood glucose concentrations change in the postprandial period (reviewed in reference 8). High-GI meals produce greater postprandial insulin concentrations and C-peptide excretion than do nutrient-controlled low-GI meals. Observational and interventional studies have linked GI to the risk of obesity, diabetes, heart disease, and cancer, although the topic remains much debated. One factor contributing to this ongoing controversy is the relative paucity of data regarding the relevant molecular mechanisms. If differences in insulin secretion mediate the genetic effects observed by Kallio et al, similar effects would be expected to occur with both low-GI and high-GI diets. This possibility is supported by a human study and several rodent studies, which showed potentially beneficial changes in the expression of HSL and other relevant genes with a low-GI diet (8, 9).

Several methodologic issues should be considered in the interpretation of this study. Microarray analyses have well-known technical limitations and statistical problems, especially when involving small sample sizes (10). The unidirectional change in gene expression within each diet group provides some grounds for concern, although confirmation with quantitative polymerase chain reaction provides reassurance on this point. In addition, many of the observed changes occurred in genes that have a pathophysiologically relevant relation to diet and disease, which provides further confidence in the study. In any event, these findings need to be confirmed and extended by additional research.

Molecular pathways involved in hormone action have been the target of a multibillion-dollar pharmaceutical research effort. However, many of these pathways may normally be under dietary regulation. The results of the present study emphasize the age-old wisdom to "use food as medicine"—in this case, for the targeted prevention and treatment of obesity, diabetes, and heart disease.

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DSL is the author of *Ending the Food Fight*, a book on childhood obesity.

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