Obesity: Common Symptom of Diverse Gene-Based Metabolic Dysregulations

Pathophysiology of Obesity

Jules Hirsch
The Laboratory of Human Behavior and Metabolism, The Rockefeller University, New York, NY 10021–6399

In spite of extraordinary efforts to educate the public about the hazards of obesity, this unfortunate disorder is increasing in prevalence, particularly in lower socioeconomic groups in the United States. A variety of commercial efforts that offer diets, behavior modification and programs of physical activity have not stemmed the tide. There is an increasing interest in drug therapy. However, all currently available drugs have not been adequately tested for efficacy and potential adverse effects over long periods of time. Furthermore, drug treatment rarely leads to the full removal of obese weight, but only some lesser decline in body weight. Clearly, a better understanding of the pathogenesis of obesity is very much needed.

Our understanding of the pathogenesis of obesity has moved during recent decades from a careful analysis of psychosocial factors to a deeper understanding of the biology of fat storage and energy metabolism. The psychological and behavioral elements remain important because the final common act that leads to either obesity or its amelioration is the behavior of altered food intake and/or physical activity. Yet, a study of cellular and metabolic features that are important forces acting on behavior has become of increasing concern. Studies done more than 25 years ago on adipose tissue metabolism and cellularity have again become of great interest as peptides secreted by adipocytes that may affect energy metabolism have been uncovered. Furthermore, new methods for the study of energy metabolism have led to a dissection of the role of food intake vs. energy expenditure in the pathogenesis of obesity.

Remarkably, when body weight is altered by 10% in both obese and nonobese subjects, there are startlingly reproducible changes in the expenditure of energy. This was shown when subjects were studied over many months in a metabolic setting at the Rockefeller University Hospital. When body fat mass was made to increase 10% above “usual” weight, there was an unanticipated increase in energy expenditure of roughly 10 kcal/(kg·d) fat free mass. When body fat declined and was maintained at a new lower level 10% below usual body weight, a similar decrease in energy expenditure occurred and persisted. These changes lead to an approximate alteration of 15% in total energy expenditure and may be significant in the maintenance of usual body weight whether the individual is obese or nonobese. Thus, energy expenditure can vary with the level of fat storage, and this variation of expenditure may act to maintain the amount of stored triglyceride at a “set” level—but one that is obviously different in obese and nonobese subjects.

The ability to examine rodent mutant obesity by new methods of molecular genetics has uncovered the mechanism whereby these animals become obese. Interestingly, in each case, there is one element of a complex regulatory system that is defective, e.g., the elaboration and secretion of a peptide from adipose tissue or the adequacy of a central nervous system receptor for this peptide. The human system appears more complex in that simple one-gene mutations, either the mutations found in rodents or other mutations, are rarely found to be the “cause” of human obesity; yet, genetic factors have been repeatedly indicated as potent elements in the pathogenesis of human obesity.

Utilizing the data from molecular genetics will clarify important sites of regulation of fat storage in humans. How fat storage becomes set at higher and lower levels and how it resists changes will draw on the newly available molecular genetic data. Now there is hope that the regulatory scheme for energy metabolism can be sufficiently well defined to understand the pathogenesis of human obesity.

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2 This is a slightly expanded version of an abstract that was distributed at the symposium. Full manuscript was not received.