Understanding obesity: The interaction of diet, genetics, and hormones

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The widely-held belief that gluttony and sloth underlie all obesity is fading, as research sheds light on the interactions between diet, genetics, hormones, and neurotransmitters. Treatment of this ever-increasing problem is limited by a high rate of recidivism after diet or other therapies. The clinician often encounters a paradox: patients who do not need to lose weight can lose weight, while those who need to cannot.

Understanding the etiology of obesity may lead to better treatments, but we are only beginning to understand this complex and heterogeneous condition.

NEUROTRANSMITTERS AND CRAVINGS

Different neurotransmitters are thought to regulate craving for each of the different macronutrients: protein, carbohydrates, and fat. Low serotonin levels in the brain cause craving for carbohydrates, and carbohydrate intake raises serotonin levels, decreasing carbohydrate craving but increasing craving for protein. Protein intake has the opposite effect, causing increased intake of carbohydrate at the next meal and decreased intake of protein.[1]

Of interest, obese persons who claim to crave carbohydrates eat a normal amount and variety of food at mealtimes (about 1900 calories/day), but also consume an additional 700 to 1000 calories/day as carbohydrate-rich snacks. A theory is that such persons have a mild form of depression and use snacks as a form of self-medication to increase their serotonin levels.[1]

THE MANY PERILS OF FAT

Eating too much carbohydrate can lead to obesity, but eating too much fat is worse, because in terms of calories needed to store in the body, fat is much more economical. Dietary carbohydrate is digested, transported, and stored at a cost of 7% of ingested carbohydrate calories; converting carbohydrate into fat takes another 23%. However, storing dietary fat as body fat takes only 3% of the fat calories ingested.[2]

Further, dietary fat does not help regulate the appetite during eating. Low-fat, high-fiber foods produce satiety at about half the calories as do high-fat foods. Thus, if people eat high-fat foods, they take in more calories. More alarming, many obese persons have difficulty sensing when they are full. Also, people eat high-fat foods faster (because these foods are usually easier to chew), and are more likely to eat to discomfort when consuming a high-fat meal.[2]

THE ROLE OF EXERCISE

The role of exercise — or lack thereof — is one of the most difficult factors to assess in obesity. One study demonstrated that adolescent males who watched little television were more physically fit than those who watched more, but the latter were not necessarily more obese.[3] It is hard to generalize these findings, because most obese persons are not adolescent males and consequently do not have the same high metabolic rate.

Exercise programs in which obese adults lost weight required them to exercise far more than most obese persons will. Further, a major flaw in these studies was their high dropout rates: only very motivated persons succeeded.[4]

The data on combining diet and exercise are mixed, but Bray[5] put it best when he wrote: "...in the longer term, many people who successfully maintain a lower body weight do so by increasing their exercise." So rather than using exercise to lose weight, it seems more prudent to use it to maintain weight loss achieved by diet.

GENETICS AND METABOLISM DURING WEIGHT LOSS

Unfortunately, when an obese person begins to lose weight, the body tries to maintain its level of body fat by decreasing its energy expenditure, which may remain low for up to 4 years.[6] Genetic and hormonal influences may play a role in this effect.

Many studies compared percentages of

body fat and lean body mass in twins and siblings. Monozygotic twins are most similar,[7] but adopted children also have strong correlations in body composition with their biological parents. These correlations are seen across a range of percentages of body fat, as one would expect if multiple genes are involved.[8]

However, environment does have an effect, especially in Western society, which enjoys readily available palatable food in large quantities. For example, in one study, twins reared apart were less similar in body composition than would be expected if body type were simply a matter of genetics.[9]

IS THERE A SETPOINT FOR WEIGHT?

Two important observations indicate there is a "setpoint" (sometimes called "adipostat")[10] for weight: obese persons who lose weight tend to drift back into obesity, and patients treated for hyperthyroidism return to their premorbid weight after thyroid function is normalized.[11]

The role of leptin and neuropeptide Y in regulating appetite and metabolism

Studies in animals have shed some light on how this adipostat works.[10] In brief, fat cells produce a hormone called leptin that acts on the brain to tell the animal to stop eating (by complex endocrine controls that may include decreasing levels of a hormone called neuropeptide Y) and to increase energy use.[12] Mice lacking the gene that codes for leptin are obese.[13]

Leptin reduces obesity in some mice

Leptin administration reduces body weight in obese mice lacking the leptin-coding gene and in lean mice. It also decreases glucose and insulin levels, adiposity, and food intake in obese mice, but not in lean mice. Further evidence that leptin is not just an appetite suppressant is that it normalizes oxygen consumption, body temperature, and locomotor activity in obese mice.

Other mice are resistant to leptin

In contrast, another strain of obese mice has high leptin levels and may in fact be resistant to it. This mouse is also diabetic and has high insulin levels.[14] When these mice are given leptin, they do not lose weight or decrease their intake. Much like these mice, obese humans have increased expression of the leptin-coding gene,[15] but this may not necessarily be an indication that all obese humans are leptin-resistant.

Humans and leptin

Recently, Considine[16] found that leptin is detectable in human serum by radioimmunoassay, serum concentrations of leptin are significantly higher in obese subjects, there is a strong positive correlation between serum leptin concentration and percentage of body fat, and correlations exist between serum leptin concentration and body mass index, fasting serum insulin, and age. When obese patients in this study lost weight, leptin levels decreased, as did mRNA coding for leptin in adipocytes. Leptin levels did not rise significantly during weight maintenance, nor did they change before or after meals.

THE FUTURE OF LEPTIN IN TREATING OBESITY

Humans are heterogeneous with respect to obesity. Obese persons who are not leptin-resistant (ie, who have diet-induced obesity), may lose weight when given leptin. Other obese persons may resemble the diabetic mouse, having naturally high leptin levels and leptin resistance. In these patients, leptin may not be a useful treatment.

If leptin proves useful in humans, it will be in great demand and may even have potential to be a drug of abuse in persons with altered body image. ■

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