Obesity and overweight are among the biggest public health challenges in the U.S. (13). They are also increasing rapidly throughout the world, and many countries are on an obesity trajectory that is tracking that seen in the U.S., but with a 10- or 20-year time delay (http://www.oecd.org/els/health-systems/Obesity-Update-2014.pdf). Additionally, the treatment of obesity is daunting. Most people who lose weight regain it, there is no widely used safe and effective pharmacological therapy, and the only medical intervention that works consistently is bariatric surgery.

Causes of the Obesity Epidemic

The causes of the obesity epidemic are almost certainly multifactorial. In the U.S., it started in the middle 1970s or perhaps 1980, and because the changes have occurred so rapidly, it is unlikely that fundamental changes in the genome caused them (http://win.niddk.nih.gov/statistics). Instead, factors including reduced population-based levels of occupational and leisure-time physical activity, more calorie consumption (controversial), changes in macro-nutrient composition, and reductions in smoking rates have all played some role. There is also emerging evidence for so-called maternal fetal programming as a contributor to obesity (4). In this context, some authors have argued that the primary cause of obesity has been changes in calorie consumption or alterations in macro-nutrient composition in the diet (15). Other investigators have focused more on the loss of both occupational and leisure-time physical activity (3, 9). Of note, common gene variants associated with obesity cause only modest differences in body weight, and the association is much less robust in physically active individuals (12). This latter finding highlights the interactions between what we eat and how much we do as major determinants of how much we weigh vs. genetics per se. In other words, genotype does not equal phenotype when it comes to garden-variety human obesity.

Animal Models Do or Don’t Recapitulate Human Data?

Against this short summary of the human data, it is not unusual to see headlines about a study in a high-profile journal reporting that an obesity gene or pathway has been identified in an animal model that “causes” obesity (1). In these models (typically rodents), either selectively bred animals or genetically engineered animals are studied. They are provided ad lib or high-fat diets, live in social isolation, and are not provided access to either structured periods of exercise or voluntary running wheels. Thus, unlike humans, in the commonly studied animals, there is a strong genotype-phenotype link and typically a limited range of physical activity, dietary choice, and social interaction.

The obvious question then is what happens when the animals are exposed to more human-like conditions. In the case of voluntary physical activity via running wheels, frequently the obesity phenotype either does not emerge, is attenuated, or some other facet of obesity-related pathophysiology is prevented (5, 11). When rodents are fed so-called cafeteria diets (or other highly palatable food), they get fat, but again exercise attenuates the emergence of the obesity phenotype or some facets of obesity-related pathophysiology (2). These latter points highlight the role of exercise in preventing obesity and especially the successful treatment of it (14). These findings might also explain in part why less palatable diets that restrict food choices seem to work at least in the short run for humans.

There appears to be less known about how the social arrangements of rodents influence body weight and feeding behavior by members of the group. However, population-based studies in humans suggest that the “who-you-know-ome” has a lot to do with health behaviors including obesity (8). In a related context, at least one rodent model associated with longevity seems to do worse when living in a colony vs. the more typical caged environment (7). So, perhaps social stress trumps genetics in that situation. Additionally, most rodents are housed at temperatures below thermoneutral, which influences both food intake and metabolism (10).

Creative and Combination Models Needed?

When I started thinking about this essay, my preexisting bias was that animal models to study obesity might have limited translational value for the human condition due to relative genetic homogeneity, limited dietary variety, limited physical activity, limited social interaction, and other environmental factors. However, as I dug deeper, the striking thing is the extent to which studies that used approaches like the cafeteria diet and voluntary exercise have in fact largely recapitulated the human observations. It seems to me that clever studies on social and other interactions, feeding behavior, exercise, environment, and obesity are perhaps the next step. The fascinating observations in hamsters on social defeat and feeding behavior are just one example of how some of the potential interactions might be explored (6).

Summary

Human obesity is a complex phenomenon where economic, cultural, behavioral, and biological factors intersect in the physiological space. Developing animal models that capture several elements of the many potential interactions between these factors will only increase their translational value.

References


