Obesity and associated type 2 diabetes mellitus are the emerging epidemic of this new century. Identifying the key mechanism of the pathophysiology offers unique insights into potential prevention and therapy. One of the classic animal models of obesity and insulin resistance has been the ob/ob mouse. Zhang et al. set the scientific world a-buzz in 1994 with the discovery that the obesity (ob) gene product was in fact leptin, and leptin deficiency accounted for the obesity in these mice.

Leptin is secreted by the fat cells, along with other tissues, to act on the hypothalamic leptin receptors (Ob-Rb) to decrease food intake and increase energy expenditure in the host. Under physiological conditions, the amount of leptin produced by fat tissues is directly related to the mass of adipose tissues. Both leptin deficiency (ob/ob mice) and leptin resistance (db/db mice having a defective leptin receptor) lead to hyperphagia and decreased energy expenditure in the host (Figure 1). Predictably, this leads to obesity, the insulin resistance type of diabetes, and a decrease in lean body mass. Correction of leptin deficiency in the ob/ob mouse causes a marked reduction in food intake and a normalization of its weight.

The biological actions of leptin are mediated largely through interactions with its cognate receptor expressed in the hypothalamus. Subsequent studies demonstrated that leptin receptors (Ob-R) have a widespread tissue distribution including liver, kidney, lungs, pancreas, and heart. Correction of leptin deficiency in the ob/ob mouse causes a marked reduction in food intake and a normalization of its weight.

The study by Barouch et al. in this issue of Circulation has identified a novel direct link between leptin and cardiovascular structural remodeling. Barouch et al. have found that leptin deficiency in the ob/ob mice in fact led to ventricular hypertrophy. The degree of hypertrophy is independent of body mass. Most interestingly, exogenous administration of leptin in this primary leptin deficiency model reduces the ventricular hypertrophy very quickly. This suggests that the leptin receptors, which are present in the myocardium, may also have a primary remodeling effect.

How do we reconcile the fact that in this laboratory setting, leptin deficiency actually leads to ventricular hypertrophy, yet clinically, ventricular hypertrophy is found in the presence of elevated levels of leptin? The observation by Barouch et al. is perhaps best considered in light of nature’s original role for leptin. There is now a shifting paradigm that leptin is...
a hormone that was more designed for periods of nutritional deficiency rather than nutritional excess. Thus, when there is a general decrease amount of caloric intake in a host, there are fewer fat stores and hence less leptin. The lower levels of leptin decrease the hypothalamic leptin receptor occupancy, leading to a conservation of energy metabolism and an increased appetite for food. This of course is an important self-preservation and survival strategy. In this setting of self-preservation, there is a redistribution of lean muscle mass by decreasing the peripheral muscle bulk while preserving or increasing central organ’s mass.

So what is the implication of the hypertrophy process that Barouch et al.20 have found in the setting of secondary leptin deficiency or leptin receptor resistance, as commonly found in patients? We now have a paradoxical situation in which we no longer have nutritional deficiency, but rather have a nutritional excess. This triggers a series of metabolic adaptations that are counterintuitive from nature’s point of view. To protect us from excessive leptin increase, the body has upregulated pathways that will lead to decreased receptor sensitivity. This therefore paradoxically produces a state of relative leptin deficiency despite elevated leptin levels. Unfortunately, from the cell’s point of view, this relative lack of leptin signaling will lead to hypertrophy, thus accounting for the hypertrophy that we see in patients with obesity, type 2 diabetes, or hypertension.

Therefore, a lesson from the study by Barouch et al.20 is that leptin has wide-ranging tissue remodeling implications. Unfortunately, in our current era of excessive caloric intake, what was designed originally to prevent us from starvation now comes back to haunt us as the body secondarily tries to protect us from caloric excess. Therefore, the solution for the left ventricular hypertrophy in remodeling in obesity is not necessarily through leptin infusion, even though if one administers enough leptin to overwhelm the receptors, there will probably be a temporarily regression. However, this is not pathophysiological rational. The more appropriate strategy will be to correct the original abnormalities that originally led to the receptor downregulation and insensitivity. This involves weight reduction, caloric restriction, restoration of metabolic receptor sensitivity, and reversal of many of the abnormalities that triggered the body to develop these secondary defensive maladaptations. Ultimately, we cannot fool mother nature, but we can work with her original design.
Figure 2. The differences between and similarities of leptin receptor insensitivity and leptin resistance. This is the most common situation found clinically. In the setting of caloric excess and obesity, phosphorylation of the leptin receptor leads to decreased leptin signaling, thus creating a secondary or relative leptin deficiency. This is often accompanied by insulin receptor insensitivity, or the metabolic syndrome. The cross talk between the 2 systems similarly will lead to increased food intake and further obesity. This also leads to ventricular hypertrophy and autonomic overactivity. The increase in associated autonomic activity is thought to be balanced by the nitric oxide production in the peripheral blood vessel. Ins indicates insulin; P, phosphorylation; and IRS, insulin receptor substrate. Other abbreviations as in Figure 1.

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