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 abuzz 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. This predicts that leptin will have a wide ranging influence on metabolism and possibly also cardiac structure and function. In contrast to primary leptin deficiency observed in the ob/ob mouse, in the clinical setting, the most common leptin abnormality in patients is “receptor insensitivity,” leading to secondary circulating leptin excess and peripheral leptin resistance. A good analogy for this condition is type 1 versus type 2 diabetes mellitus. Type 1 diabetes represents primary insulin deficiency (similar to primary leptin deficiency in the ob/ob mice), where judicious replacement of insulin (or leptin) can largely correct the underlying condition. However, in the more common type 2 diabetes, where there is insulin receptor downregulation and insulin resistance, there is a compensatory increase in circulating insulin and a decrease in effectiveness of insulin treatment. A better treatment strategy in this latter setting is the reversal of the factors that originally led to the insulin resistance.

Indeed, in the commonest clinical settings of leptin resistance or leptin receptor insensitivity, there is also concurrent insulin resistance or insulin receptor insensitivity (Figure 2). This insulin resistant state is well recognized in obesity, hypertension, and heart failure and after myocardial infarction. In these settings, circulating leptin levels are elevated, and in fact the serum leptin level is an independent predictor for cardiovascular morbidity and mortality in these conditions. In this case, leptin becomes a marker for the degree of receptor resistance and the underlying severity of the metabolic derangement. Furthermore, fasting plasma leptin levels are associated with increased myocardial wall thickness, independent of body weight composition and blood pressure levels. Not surprisingly, leptin also directly affects insulin sensitivity by regulating the efficiency of insulin-mediated glucose metabolism by the skeletal muscle.

Because leptin binding sites have been found in brain regions that are important in cardiovascular control, there is a reason to suspect that leptin may affect cardiovascular function through its effects on the central nervous system. Current hypotheses suggest that leptin may have a balanced effect on blood pressure, with a central stimulatory effect through sympathetic activation and a local depressor effect attributable to local nitric oxide release.

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 organs’ mass.

So what is the implication of the hypertrophy process that Barouch et al20 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 al20 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 pathophysiologically 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 1. Circles of feedback in primary leptin deficiency. This is the situation found in ob/ob mice, or rare human genetic mutations. In this setting, the adipose tissue will not be able to elaborate leptin commensurate with the fat tissue mass. This leaves the leptin receptor unoccupied. The receptor signals through janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathways, with cross talk from P13 kinase (P13K) pathways. The receptor nonoccupancy leads to a number of adiposity signals, including increased food intake and decreased energy expenditure. This also leads to ventricular hypertrophy, which is correctable with leptin infusion. Metab indicates metabolism.
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 crosstalk 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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References


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