Hyperleptinemia
Protecting the Heart From Lipid Overload

Roger H. Unger

Abstract—In this review, we attempt to deduce teleologically the physiological mission of leptin. Because overnutrition and diet-induced obesity are the only known causes of hyperleptinemia, we contrast the differences in overnutrition in normally leptinized rodents, in which the added lipids are confined to adipocytes, with those of unleptinized rodents, in which the added lipids are distributed in liver, pancreatic islets, and heart and skeletal muscle, causing organ dysfunction and cell death with a disease cluster resembling metabolic syndrome. We focus here on lipid-induced cardiac dysfunction and the remarkable ability of hyperleptinemia to prevent it. We conclude that the hyperleptinemia of overnutrition prevents the ectopic lipid deposition by: (1) acting on hypothalamic appetite centers to limit the caloric surplus to fit the available adipocyte storage capacity and, (2) upregulating of fatty acid oxidation and downregulating lipogenesis in peripheral tissues to minimize ectopic lipid deposition. The causes of failure of this system and its clinical consequences are discussed. (Hypertension. 2005;45:1031-1034.)

Deducing the Function of Hyperleptinemia
One decade after its discovery,1 the precise physiological function of the adipocyte hormone leptin has still not been unequivocally established. Nonetheless, there are potentially important clues. The physiological mission of a hormone can often be deduced from its secretory behavior (ie, an analysis of factors or situations that elicit its hypersecretion). Because the only known cause of leptin hypersecretion is diet-induced obesity (DIO), it can be inferred that hyperleptinemia plays an important physiological role in DIO. The storage of surplus calories as fat provides a vital means of prolonging survival during famine,2 so long as the caloric surplus does not jeopardize health before the famine has even begun. The putative tradeoff is as follows. To survive famine, one must have stored a stockpile of calories in the form of triglycerides. Yet most cells in our body are intolerant to lipid overload and are seriously damaged by certain lipid metabolites.3 The evolution of the adipocyte, a cell that is uniquely adapted to store enormous quantities of triacylglycerol (TG), resolved this critical problem by providing the requisite caloric storage compartment. However, there remained the problem of protecting nonadipose tissues from lipid overaccumulation as adipocytes undergo expansion through hypertrophy and hyperplasia in the defense against famine. This concept of the role of leptin is supported by the fact that in syndromes of congenital leptin deficiency and leptin resistance, widespread ectopic lipid deposition and severe lipotoxicity appear early in life and can be ameliorated with leptin treatment.4–8

Leptin deficiency states are extremely rare, the most common form being congenital generalized lipodystrophy, which is caused by the lack of leptin-secreting adipocytes. Early in life, patients develop a severe facsimile of metabolic syndrome, or with insulin resistance, hyperleptinemia, severe diabetes, cardiomyopathy, and fatty liver. These abnormalities can be dramatically ameliorated with leptin treatment.8 A second, much rarer form of leptin deficiency is caused by a mutation in the leptin gene.9 It is associated with severe obesity.

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Evidence for Leptin-Dependent Lipid Partitioning
The problem of lipid partitioning was resolved through the evolution of leptin. Leptin achieves compartmentalization of surplus lipids in 2 ways: (1) it limits the level of overnutrition via hypothalamic action on appetite centers to keep the intake of surplus calories from exceeding the slowly expanding lipid storage capacity of adipocytes and; (2) it upregulates the fatty acid oxidative capacity in nonadipose tissues so as to oxidize any lipid spillover that may have occurred during the period of overnutrition, while reducing their lipogenic capability.4 The fact that lipotoxicity is usually absent early in the course of DIO is consistent with the idea that the hyperleptinemia generated by overnutrition is effectively protecting the nonadipose tissues from lipid overaccumulation as adipocytes undergo expansion through hypertrophy and hyperplasia in the defense against famine. This concept of the role of leptin is supported by the fact that in syndromes of congenital leptin deficiency and leptin resistance, widespread ectopic lipid deposition and severe lipotoxicity appear early in life and can be ameliorated with restoring leptin action.4–8

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mutation of the leptin receptor gene Lepr-b is extraordinarily rare, it has been reported in man.10 Acquired leptin resistance, in contrast, may be one of Western man’s most prevalent conditions. Virtually all obese individuals are resistant to actions of this versatile hormone.

**Failure of the Antilipotoxic Action of Hyperleptinemia**

The common obesity-related disorders that afflict a major segment of the American population are the result of the chronic overnutrition and underexertion that has become the prevalent US lifestyle. The disease consequence (ie, the metabolic syndrome) generally appears in middle age as a result of failure of hyperleptinemia to carry out the 2 putative functions mentioned above. Such failure can be the result of “supersizing,”11 in which food intake exceeds the satiety level and the available triglyceride storage space, or it can be an age-related decline in leptin secretion or leptin responsiveness.12 The consequence of such liporegulatory failure, whatever its cause, is steatosis, the accumulation of lipids in organs such as liver, pancreatic islets, skeletal muscle, cardiac muscle, and probably other nonadipose tissues. The result is dysfunction of the affected cells, or “lipotoxicity,”13 which may be followed by lipoid-induced programmed cell death, or “lipoapoptosis.” The clinical pathological consequences of the widespread steatosis include nonalcoholic steatohepatitis, type 2 diabetes,14 insulin resistance,13 and lipotoxic cardiomyopathy.14 The latter diagnosis is not currently recognized by clinicians, in part because it is so often overshadowed by its far more easily diagnosed companion lipid derangement, coronary artery disease. However, spontaneously occurring lipotoxic cardiomyopathy has been identified in leptin-unresponsive Zucker diabetic fatty rats14 and has been transgenically induced in mice by overexpressing acyl coenzyme A (CoA) synthetase in their cardiomyocytes.15 In both models, dilated cardiomyopathy attributable to lipid-induced apoptosis of cardiomyocytes leads to premature death. Recent studies in presumably healthy obese humans suggest that it may also commonly occur in man. Using magnetic resonance spectroscopy, Szczepaniak et al reported a positive relationship between body mass index and intracardiacmyocyte fat and a negative relationship with systolic function.16 Elegant studies of Taegtmeyer’s group have identified intramyocardial lipid deposition with contractile dysfunction and heart failure.17

**Testing the Antilipotoxic Hypothesis**

To test the hypothesis that the hyperleptinemia of DIO reduces ectopic lipids, we used the model of severe myocardial steatosis and lipotoxicity induced by transgenic, cardiomyocyte-specific overexpression of the acyl CoA synthetase (ACS) gene.15 These mice are normal except for severe lipotoxic cardiomyopathy, caused not by defective leptin action, but by increased import of fatty acid into cardiomyocytes. The potential mechanisms by which unoxidized fatty acids may cause damage to cells are depicted in Figure 1. In cardiomyocytes, as in pancreatic islets, the pathway of de novo ceramide synthesis seems to be the most important

destructive avenue based on the fact that its interruption prevents the apoptosis.

The transgenic mice with cardiac ACS overexpression develop echocardiographic evidence of severe left ventricular dysfunction, biochemical and electron microscopic evidence of ectopic lipid deposition, and histological evidence of myofiber disorganization and interstitial fibrosis. The mice die prematurely with a dilated cardiomyopathy.15 Because the mice are not obese, their leptin levels are not high (ie, they lack the antilipotoxic protection postulated for hyperleptinemia).

If the function of hyperleptinemia is, in fact, to protect against ectopic lipid deposition, induction of DIO level hyperleptinemia in these lean, normoleptinemic transgenic mice should prevent their lipotoxic cardiomyopathy. To simulate the hyperleptinemia of DIO, we treated 6-week-old ACS-transgenic mice with recombinant adenovirus containing the leptin cDNA (AdCMV-leptin). As a control, we administered adenovirus containing β-galactosidase cDNA (AdCMV-β-gal). During the first week after AdCMV-leptin treatment, plasma leptin levels ranged between 40 and 50 ng/mL, well above the 4 ng/mL levels reported previously in rats at the start of a high-fat diet.8 However, at 8 weeks after AdCMV-leptin treatment, leptin levels had declined to 11.1 ± 0.45 ng/mL,18 well below the ∼25 ng/mL mean leptin level observed after 10 weeks of high-fat feeding.4 Leptin levels averaged 1.2 ± 0.06 ng/mL in AdCMV-β-gal–treated ACS-transgenic control mice and in untreated wild-type controls. Using methods described previously, we compared the hearts of hyperleptinemic and normoleptinemic transgenic mice.19

Severely dilated cardiomyopathy was grossly apparent in normoleptinemic ACS-transgenic control mice (Figure 2A), confirming the original observation of Chiu et al.15 There was marked hypertrophy and dilatation of all chambers, with a doubling of heart weight and the heart weight/body weight ratio compared with the wild-type group. In striking contrast,
the hearts of hyperleptinemic ACS-transgenic mice were normal in size, appearance, weight, and heart/body weight ratio. Transthoracic ECGs in AdCMV-β-gal–treated ACS-transgenic mice revealed markedly impaired systolic cardiac function with depressed fractional shortening on M-mode images and thickening of the anterior and posterior walls of the left ventricle (Figure 2B). The fractional shortening was normal in AdCMV-leptin–treated ACS-transgenic mice (Figure 2C). In contrast, the hyperleptinemic ACS-transgenic group exhibited normal fractional shortening. Hematoxylin and eosin staining of hearts of control ACS-transgenic mice revealed myofiber disorganization, enlarged cardiomyocytes, and interstitial fibrosis (Figure 3Ab). Trichrome stains highlighted the collagen deposits in the subendocardium and interstitium. Myocytes had large unilocular vacuoles, consistent with lipid droplets, resembling adipocytes (Figure 3Bb). AdCMV-leptin–treated ACS-transgenic mice hearts were morphologically indistinguishable from the wild-type hearts.

The lipotoxicity of mice with ACS overexpression is caused in large part by increased import of long-chain fatty acids synthesized previously, rather than by increased lipogenesis or decreased oxidation in the cardiomyocytes themselves, as is the case in other forms of lipotoxicity. Seven days after treatment, the mean plasma levels of TG and free fatty acid in the hyperleptinemic mice were less than half of normoleptinemic controls, thereby reducing a source of imported fatty acids. But there was also evidence that hyperleptinemia had altered lipid metabolism within the heart in the direction of antiligogenesis. This took the form of increased phosphorylation of the key enzyme of lipid metabolism, AMP-activated protein kinase (AMPK). This may have contributed to the reduction in cardiac TG content by inactivating acetyl CoA carboxylase, thereby reducing malonyl CoA, the first committed step in fatty acid synthesis and an inhibitor of fatty acid oxidation. In addition, the expression of the lipogenic enzymes fatty acid synthase and glycerol-phosphate acyl transferase mRNAs was significantly lower in the hearts of hyperleptinemic ACS-transgenic mice, consistent with the dramatic decrease in cardiac TG content. Finally, a major factor in preventing lipoapoptosis may have been the >2-fold increase in expression of the antiapoptotic factor Bcl2 in the hearts of hyperleptinemic ACS-transgenic mice, coupled with a 50% decrease in expression of proapoptotic Bax.

**Clinical Perspectives**

There is now much correlative evidence to suggest that the lipoxic disorders of rodents share a common etiology with metabolic syndrome of humans, as has been reviewed previously. If so, the principal role of leptin may be to prevent metabolic syndrome by maintaining normal liporegulation despite enormous dietary variations, much as insulin prevents diabetes through maintaining normal glucoregulation despite the same dietary variations. From this perspective, both hormones are homeostatic regulators that seek to maintain metabolic homeostasis and cellular health despite the challenging perturbations that characterize our existence. Ultimately, as life nears its end, the homeostatic systems will fail. But depending on the magnitude and duration of perturbations and genetic determinants, this will not occur until late life, long after the reproductive years, thereby assuring species survival.

The findings cited here provide strong support for a protective role of leptin against lipotoxicity. By elevating plasma leptin levels of these normoleptinemic lean mice destined to develop lipotoxic cardiomyopathy, we completely prevented all manifestations of their severe disease, its abnormal echocardiographic patterns, its elevated cardiac TG content, and its cardiomyocyte hypertrophy, fat droplets, and interstitial fibrosis.

Can this information be translated to patient care at the present time? To the cardiologist, lipotoxic cardiomyopathy is a completely unfamiliar entity. However, it may explain certain cases currently being diagnosed as idiopathic cardiomyopathy and congestive failure. Lipotoxic cardiomyopa-
thy is more easily treated than diagnosed. Striking improvement during stringent caloric restriction may at present be the only available diagnostic test as well as therapeutic strategy. Definitive noninvasive diagnosis requires sophisticated techniques of magnetic resonance spectroscopy\(^{16}\) that are not generally available. Trials of AMPK activators, which have been successful in rodent models,\(^{23}\) have not yet been studied in man.

**Discussion**

Lipotoxicity is believed to be a generalized multiorgan problem. There is evidence that the pulmonary dysfunction in leptin-deficient ob/ob mice is ameliorated by leptin therapy.\(^{24}\) Whether or not lipotoxicity of pulmonary tissues contributes to the respiratory problems associated with human obesity is a question that has not yet been explored. Also, the prominence of hypertension in obesity-related metabolic syndrome raises the question of lipid deposition in the peripheral arterioles as a cause of increased peripheral resistance. If the components of the metabolic syndrome represent a decompensation of an antilipotoxic homeostatic system, in which leptin is a key player, recompensation might be achievable through therapeutic strategies that include elimination of the nutrient perturbations and pharmacological activation of the leptin signal transduction pathways, particularly AMPK, in the affected organs.

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**References**

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