

Diet-Induced Leptin Resistance: The Heart of the Matter

The recent decision to ban trans fatty acids (trans fats) in New York City and European countries such as Denmark has made clear how, in our society, high-fat foods have become almost synonymous with a bad influence on health. Although the exact mechanistic links remain to be understood, a high-fat diet is known to cause obesity and to, subsequently (or in parallel), damage glucose homeostasis and cardiovascular systems (1, 2). One of the more accepted molecular concepts thought to explain these processes is the model of leptin resistance: exposure to a high-fat diet impairs the sensitivity and physiological response to the satiety-inducing adipocyte hormone leptin, thereby contributing to a syndrome similar to what can be observed in leptin-deficient rodents or humans (3, 4). Leptin deficiency—and presumably diet-induced leptin resistance—leads to a syndrome with increased food intake, morbid obesity, impaired glucose metabolism, and multiple other comorbidities such as a dysfunctional reproductive systems and imbalanced bone metabolism (5). Because failure of leptin treatment for diet-induced obesity has also been attributed to leptin resistance, numerous efforts are still ongoing to better understand and ultimately prevent or cure leptin resistance (3). Existing models have proposed a number of different mechanisms to explain the high-fat-diet-induced development of leptin resistance, which is thought to be a pleiotropic phenomenon, although it has mainly been examined with regard to leptin's action in the central nervous system (CNS) (6). The two most popular models explaining diet-induced leptin resistance include decreased transport of leptin across the blood brain barrier (7) and impaired intracellular leptin receptor signaling (6)—possibly a result of constant exposure to increased circulating amounts of either dietary lipids or leptin itself.

With the general wisdom being that leptin resistance is a generalized phenomenon as much as a bad thing, recent findings by Somoza *et al.* (8), published in this issue of *Endocrinology*, come as a surprise. Somoza *et al.* report that the development of leptin resistance may be a process that specifically occurs in some tissues but not in others, such as, for example, the heart. If cardiac tissue, as an example, remains sensitive for leptin, heart muscle cells would exhibit signs of markedly enhanced leptin action in response to the increased leptin levels known to occur in diet-induced obesity. To study changes in cardiac metabolism during the development of diet-induced obesity, Somoza *et al.* started out by exposing mice to a high-fat diet for 2 months and comparing these with control mice on a standard chow. As expected, mice on a high-fat diet became obese and developed high leptin levels. However, such diet-induced obesity appeared

to reflect metabolic consequences of the diet composition rather than effects of hyperphagia, because the number of consumed calories did not differ between study groups. Interestingly, fat content of the heart seemed to increase initially only, whereas after 8 wk of high-fat diet exposure there was no difference between treatment groups.

Even more intriguing, two signaling pathways associated with increased fat oxidation and known to be activated by leptin were found to be markedly up-regulated in hearts of mice that were exposed to a high-fat diet. Specifically, Somoza *et al.* (8) found protein levels of uncoupling protein-2 (UCP2) and phosphorylated AMP-activated protein kinase (AMPK) to be up-regulated, but concentrations of lactate dehydrogenase as well as lactate to be decreased, in cardiac tissue. UCPs are classically associated with nonshivering thermogenesis by brown fat. UCP1 is an integral membrane protein that is located in the mitochondrial inner membrane of brown adipocytes. Its physiological role is to mediate a regulated, thermogenic proton leak (9, 10). UCP2 and UCP3 are more recently identified UCP1 homologs that might function to control the production of superoxide and other downstream reactive oxygen species (9–11). UCP2 can be activated by free radicals and free fatty acids or thyroid hormone (T_3). UCPs regulate mitochondrial biogenesis, free radical production, and local temperature and are therefore able to influence numerous cellular processes. Recent studies have shown that UCP2 has an important part in the pathogenesis of type-2 diabetes (10). Other reports indicate that UCP2 may have important neuroprotective functions and may be a regulator of synaptic plasticity (11). Interestingly, Somoza *et al.* found UCP2 to be increased in the heart upon high-fat-diet-induced obesity and propose that UCP2 may represent one molecular pathway that seems to be involved in cardiac protection from lipid deposition.

The evolutionarily conserved serine/threonine kinase, AMPK, is an energy sensor that regulates cellular metabolism (12, 13). When activated, AMPK stimulates lipid oxidation to produce energy in numerous tissues including muscle. Recent data indicate that AMPK also is a mediator of the effects of adipocyte-derived and gut-derived hormones and peptides on fatty acid oxidation in peripheral tissues. In response to such diverse hormonal signals including leptin, ghrelin, and adiponectin, AMPK serves as a cross-talk signal integrator among peripheral tissues, as well as the CNS, in the control of whole-body energy balance (12, 13).

Interestingly, and similar to their findings on UCP2, Somoza *et al.* (8) found that AMPK phosphorylation was higher in mice chronically exposed to a high-fat diet, possibly contributing to a switch of substrate choice, promoting fat oxidation. Consistent with these findings, lactate dehydrogenase in the heart was decreased in mice after 8 wk on a high-fat diet, and lactate levels were lower in cardiac tissue of these mice. These findings again would suggest a metabolic switch from using carbohydrate to using lipids as fuel.

Abbreviations: AMPK, AMP-activated protein kinase; CNS, central nervous system; UCP, uncoupling protein.

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Because these findings would fit very well with increased leptin action in the heart (leptin activates both AMPK and UCP2), the authors hypothesized that, as expected in mice on a high-fat diet, leptin resistance may be induced in some tissues such as the hypothalamus but would not develop in others such as the heart. They tested that hypothesis by injecting leptin in mice after chronic exposure to either a high-fat or standard diet. The results confirmed, as shown by quantification of intracellular leptin-specific signal phosphorylated signal transducer and activator of transcription (6) that CNS neurons, but not heart muscle cells, had developed substantial resistance to leptin.

In summary, although it induces leptin resistance in other organs such as the CNS, exposure to a high-fat diet seems to activate leptin target pathways in heart muscle cells with unharmed, if not increased, potency. Somoza *et al.* (8) were able to show that, consistent with an important functional relevance of such increased leptin signaling, mice on a high-fat diet showed up-regulated fat oxidation pathways, and no signs of lipid deposition in the heart were detected over a 2-month study period (8) (Fig. 1).

Although these novel observations reported by Somoza *et al.* (8) offer a number of potentially important new perspectives for obesity and cardiovascular research, they also raise several new questions. One obvious question would be whether the observed phenomenon is specific for heart tissue or whether other important organs and tissues may be similarly exempt from diet-induced leptin resistance and other pathological processes associated with diet-induced obesity. The provocative findings presented by Somoza *et al.* further emphasizes that future studies are needed to carefully dissect the tissue specificity and time course of leptin resistance and metabolic pathophysiology associated with the development of high-fat-diet-induced obesity. Particularly relevant in that regard would be skeletal muscle and liver, where little is known about the general importance and time-resolved in-

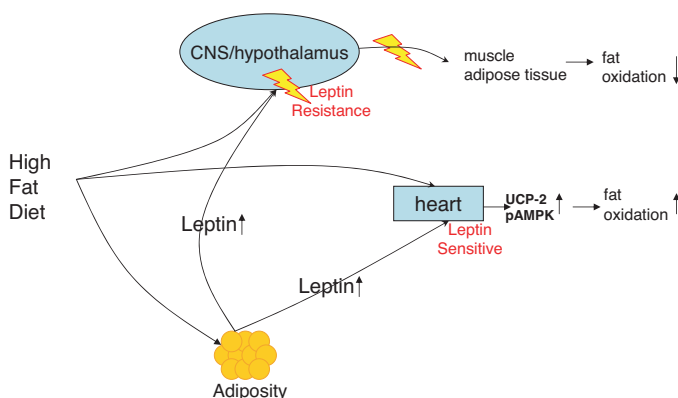


FIG. 1. Chronic exposure to a high-fat diet induces leptin resistance in the CNS but appears to activate leptin target pathways in heart muscle cells with unharmed, if not increased, potency. Somoza *et al.* (8) show that, consistent with an important functional relevance of such increased leptin signaling, mice on a high-fat diet showed up-regulated fat oxidation pathways and no signs of lipid deposition in the heart. Specifically, the authors report that cardiac levels of UCP2 and phosphorylated AMPK increase upon chronic exposure to a high-fat diet. These effects may be a consequence of increased circulating leptin levels, which, due to tissue-specifically maintained leptin sensitivity in cardiac muscle cells, protect the heart from lipid deposition.

volvement in the development of the leptin resistance syndrome.

One difficulty with the interpretation of the provocative, but largely descriptive, dataset presented by Somoza *et al.* (8) is the lack of a clear causal link between 1) increased leptin levels, 2) maintained or even increased activity of pathways promoting fat oxidation in the heart, and 3) cardiac protection from lipid deposition. Although a functional relationship seems entirely possible, data, for example, from leptin-deficient mouse models and the use of tissue-specific mouse mutagenesis for cardiac UCP2 and AMPK would be necessary to prove the hypotheses proposed by the authors. Furthermore, it is known that circulating levels of multiple other signaling factors are changed during development of high-fat-diet-induced obesity (*e.g.* insulin, resistin, adiponectin, ghrelin, IL-6, and others) (14). Several of these circulating endocrine signals are not only known to play a role in the control of energy metabolism but also in the regulation of UCPs and AMPK (12, 13).

Moreover, although it is an intriguing observation that triglyceride content of cardiac tissue was found to be normal after exposure to a high-fat diet, it would be interesting to investigate changes of parameters reflecting heart function such as heart muscle shortening or ejection fractions. If monitored at several time points during development of diet-induced obesity and in connection with changing levels of enhanced or blocked leptin, UCP2, and AMPK signaling, important insight could be gained regarding the role of leptin pathways as potential drug targets for the prevention and treatment of cardiovascular disease. Finally, if the intriguing speculations proposed by Somoza *et al.* are correct, lipid deposition and toxicity should be no issue for cardiac tissue in diet-induced obesity. Although this may be an area in which important data sets are still missing to allow for clear answers, morbidly obese patients certainly do not seem to be protected in any way against cardiovascular complications by their hyperleptinemia. Perhaps, at least for the initial phase of exposure to a high-fat diet, maintained leptin sensitivity and increased leptin action in cardiac tissue does boost fat oxidation, thereby protecting the heart as an organ of most vital importance. It does seem intriguing to speculate whether such a phenomenon would be pure coincidence or a physiological defense mechanism triggered by CNS nutrient sensors that detect increased levels of circulating fatty acids and in turn stimulate leptin expression and secretion, ultimately to protect peripheral organs from ectopic lipid deposition. Although such a model is not novel and had been proposed before, Somoza *et al.* (8) provide evidence indicating that such a mechanism may, at least to some extent and for an initial time period, actually be successful.

Although the observations of Somoza *et al.* involving UCP2 in cardiac protection from diet-induced obesity and its potential link with leptin action are new, a previous series of groundbreaking findings from Unger and colleagues (15–17) has paved the way for the studies presented here. Several studies from that group examined lipid-induced cardiac dysfunction and the ability of hyperleptinemia to prevent it. Additional aspects resulting from their work include an involvement of hypothalamic appetite centers and down-reg-

ulation of lipogenesis in peripheral tissues to minimize ectopic lipid deposition. Interestingly, findings similar to what is discussed here regarding leptin's effects on cardiac lipid deposition have been reported for lipid toxicity in lung tissue, which occurs in leptin-deficient ob/ob mice and can be corrected by leptin replacement therapy.

Despite several open questions, the studies reported by Somoza *et al.*, together with earlier studies by Unger and colleagues, provide a unique connection between the energy balance regulation and the cardiovascular consequences of a high-fat diet and obesity. The data suggest that the pathophysiological mechanisms leading to leptin resistance must rely on tissue-specific mechanisms such as impaired blood brain barrier transport. Otherwise, the lack of leptin resistance in cardiac tissue would be difficult to explain.

It would certainly be premature to conclude that hyperleptinemia may be a functionally relevant and physiologically necessary defense with beneficial rather than damaging impact in an organism during exposure to a high-fat diet. However, the evidence provided by Somoza *et al.* (8) highlights the necessity to further study the time-resolved and tissue-specific development of high-fat-diet-induced changes in cellular metabolism. These data also point to the equal importance of better understanding the role of multiorgan crosstalk in the pathogenesis of diet-induced obesity to pave the way for a pharmacological prevention and treatment for obesity and resulting consequences for metabolism and the cardiovascular system. Finally, although lipotoxic cardiomyopathy may not be a familiar entity to all clinicians at this point in time, the potential benefits of dietary intervention as well as AMPK agonists that are currently under development may offer valuable strategies for intervention in the future.

Matthias H. Tschöp, David Y. Hui, and

Tamas L. Horvath

Department of Psychiatry and Obesity Research Center (M.H.T.), and Department of Pathology and Lipid Research Center (D.Y.H.), University of Cincinnati, Cincinnati, Ohio 45327; and Department of Comparative Medicine (T.H.), Yale Medical School, New Haven, Connecticut 06520

Acknowledgments

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Address all correspondence and requests for reprints to: Dr. Matthias H. Tschöp, University of Cincinnati Genome Research Institute, Department of Psychiatry, Obesity Research Center, 2170 East Galbraith Road, Cincinnati, Ohio 45327. E-mail: tschoemh@ucmail.uc.edu.

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