Uncoupling Metabolism and Coupling Leptin to Cardiovascular Disease

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In the past eight years, beginning with the discovery of leptin, there has been an avalanche of knowledge and a conceptual revolution in understanding the regulation of body fat. Central to this revolution has been the recognition that adipose tissue is a tremendously active and important endocrine and paracrine tissue. In this regard, adipose tissue is to the last decade what the endothelium was to the previous decade—a large tissue previously relatively ignored that was found with a single discovery to be of great interest and importance.

The interest in leptin focused initially on appetite, metabolism, and adiposity, but there is mounting evidence that leptin participates in sympathetic and arterial pressure regulation and in vascular biology.

Leptin increases sympathetic nerve activity to thermogenic brown adipose tissue through a central neural action. This is not surprising, but leptin also increases sympathetic activity to the kidney and extremities. This sympathoexcitatory action would be expected to increase arterial pressure.

Of perhaps greater interest to the readers of this Journal is the mounting evidence that the arterial wall is a target of leptin action. The signaling form of the leptin receptor was initially said to be expressed only in the hypothalamus, but we now know that it is also expressed in peripheral tissues.

For example, the long, signaling form of the leptin receptor is expressed in endothelial cells. Lembo et al and Vecchione et al reported that leptin stimulates increases in endothelial NO synthesis.

Leptin promotes accumulation of reactive oxygen species in human umbilical vascular endothelial cells (HUVECs). It upregulates endothelin-1 production in HUVECs. It promotes angiogenesis. And an astonishing finding: Parhami et al demonstrated that leptin regulates osteoblastic differentiation and enhances the calcification of vascular cells.

Platelets also express the leptin receptor, and leptin potentiates platelet aggregation through a novel leptin receptor–dependent mechanism. Through this mechanism, leptin is prothrombotic. Leptin deficient ob/ob mice have delayed and unstable thrombus formation after arterial injury. Leptin normalizes this phenotype.

So leptin, like insulin, has emerged as a metabolic hormone that contributes importantly to regulation of vascular biology.

We return to the arterial pressure effects of leptin, which is a focus of the study by Bernal-Mizrachi et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology. Given that leptin produces both pressor (sympathetic activation) and depressor (increased NO) actions, the integrated actions of leptin on arterial pressure are not predictable. Acutely, leptin does not consistently increase arterial pressure, but chronic infusion of leptin increases arterial pressure in rats despite weight loss, which would be expected to lower arterial pressure. In addition, transgenic mice overexpressing leptin have significantly higher arterial pressure than wild-type control mice despite decreases in body fat. These increases in arterial pressure are accompanied by increased urinary norepinephrine and are normalized after acute alpha adrenergic or ganglionic blockade. These observations suggest an integrated sympathetically mediated pressor response to leptin. There are, however, some observations that do not support a pressor effect of leptin. For example, Zhang et al recently reported that moderate hyperleptinemia produced by adenoviral gene transfer to obese mice decreased body weight but did not produce an increase in arterial pressure. Nevertheless, pharmacologic and transgenic models support a pressor action of leptin.

Leptin-deficient, obese ob/ob mice have slightly lower arterial pressure than their wild-type controls despite profound obesity that would be expected to increase arterial pressure. Administration of leptin to the ob/ob mice (so-called leptin reconstitution) increases arterial pressure despite decreases in food intake and body weight. This suggests a physiological role for leptin in arterial pressure regulation.

In contrast to the leptin-deficient ob/ob mice, agouti yellow obese mice have partial leptin resistance, compensatory hyperleptinemia, and elevated arterial pressure. There is evidence that the elevated leptin contributes to the increase in arterial pressure.

This brings us to further discussion of the manuscript by Bernal-Mizrachi et al from Semenkovich’s laboratory in this issue of the Journal.

Uncoupling proteins cause energy derived from metabolism of food to be dissipated as heat rather than stored as high-energy phosphates. Uncoupling protein-1 (UCP-1) is normally expressed only in brown adipose tissue where it regulates thermogenic metabolism. A recent study by Li et al from Semenkovich’s laboratory demonstrated that transgenic overexpression of mitochondrial UCP-1 in skeletal
Cardiovascular Actions of Leptin

- Increases endothelial NO synthesis
- Promotes accumulation of reactive oxygen species
- Upregulates endothelin-1 in endothelial cells
- Promotes angiogenesis
- Enhances calcification of vascular cells
- Potentiates platelet aggregation and thrombus formation
- Simulates sympathetic nerve activity

In the present study, Bernal-Mizrachi et al. again report that transgenic overexpression of UCP-1 in skeletal muscle of agouti yellow obese mice increased metabolism, promoted weight loss, and increased insulin sensitivity. The major new finding was that skeletal muscle overexpression of UCP-1 decreased arterial pressure, serum leptin, and urinary catecholamines. In the transgenic agouti mice overexpressing UCP-1, superimposed administration of leptin increased arterial pressure. This was not observed with leptin administration in the nontransgenic agouti obese mice. Based on this constellation of findings, Bernal-Mizrachi et al. conclude that “skeletal muscle respiratory uncoupling lowers blood pressure through a leptin-dependent mechanism and prevents insulin resistance in genetic obesity.”

The study by Bernal-Mizrachi et al. is admirable and provides novel information and provocative conclusions. As with many studies in a rapidly evolving field, it also prompts questions.

First, is the arterial pressure–lowering effect of UCP-1 overexpression in skeletal muscle greater than that observed with a comparable decrease in adipose tissue and body weight produced by other means? In other words, is there a specific arterial pressure–lowering action of UCP-1 expression independent of weight loss? These are cogent questions because the manuscript implies that increasing respiratory uncoupling in skeletal muscle is producing a specific effect that might not be observed with other forms of weight loss.

Second, although the data may be consistent with the concept that skeletal muscle respiratory uncoupling lowers arterial pressure through a leptin-dependent mechanism, the data do not establish a persuasive cause and effect relationship. For example, UCP-1 uncoupling also improved insulin sensitivity, raising the possibility that this could have contributed to the lowering of arterial pressure. A key experiment in testing the role of alterations in leptin in the arterial pressure–lowering effect of UCP-1 overexpression would be to study the effect of UCP-1 overexpression in leptin-deficient ob/ob or leptin-resistant db/db mice, both of which completely lack leptin action.

Third, Bernal-Mizrachi et al., Li et al., and Clapham et al. suggested that promoting respiratory uncoupling in skeletal muscle represents a potential treatment for obesity and its sequelae. In the current article, the authors offer “the notion that respiratory uncoupling in skeletal muscle mimics chronic vigorous exercise,” which promotes weight loss and decreases in arterial pressure. However, there are two reports that chronic exercise training decreases UCP-3 expression in skeletal muscle in humans and rodents. This decrease in UCP-3 in skeletal muscle could preserve coupled respiration to generate high-energy phosphates for muscle performance. Conversely, extreme overexpression of uncoupling proteins in skeletal muscle could deplete high-energy phosphates and impair muscle performance. Therefore, as previously emphasized by Li et al., treating obesity in humans by promoting respiratory uncoupling in skeletal muscle will be feasible only if it is possible to produce levels that protect against weight gain without compromising muscle performance.

This study heightens interest in the role of skeletal muscle uncoupling proteins in regulation of adiposity and its cardiovascular consequences, and it suggests a potential role for overexpression of skeletal muscle uncoupling protein in the treatment of obesity and related hypertension. The therapeutic potential is speculative, but any advance in understanding the biology and potential therapy of obesity merits consideration today. We are witnessing a frightening epidemic of obesity produced by the omnipresence of food and malignantly sedentary lifestyles. Fortunately, this epidemic has been paralleled in the last decade by a revolution in understanding of the genetics and biology of obesity. The therapeutic dividends have not yet accrued, but we predict that just as discovery of the renin-angiotensin system, adrenergic receptors, and calcium channels led to safe, effective therapy for essential hypertension, so will the discovery of the pathways and mechanisms regulating appetite and metabolism lead inevitably to safe, effective therapy for obesity and its adverse consequences. The emerging evidence for vascular actions of leptin indicates that the advancing avalanche of information on the new biology of obesity merits the attention of vascular biologists.

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