Role of Leptin in the Development of Cardiac Hypertrophy in Experimental Animals and Humans

To the Editor:

Barouch et al recently published a well-designed study demonstrating that left ventricular hypertrophy (LVH) occurs in mice that are either leptin-deficient (ob/ob) or leptin-resistant (db/db). They also found that systemic administration of leptin to the leptin-deficient animals attenuated LVH more than would be predicted by the leptin-induced hypophagia and weight loss. These observations suggest that leptin may have a direct inhibitory effect on cardiac hypertrophy.

We have recently examined the association between systemic leptin levels and cardiovascular indexes in a population of healthy obese and lean men. In addition to showing that the obese had greater absolute and height-indexed left ventricular (LV) mass (confirming the association between obesity and LVH in this normotensive population), we also found a positive association between serum leptin and height-indexed LV mass, which did not persist after adjustment for body mass index.

The data by Barouch et al in experimental animals corroborate our observations in humans and provide a potential pathophysiological explanation. With rare exceptions, human obesity is associated with hyperleptinemia and apparent leptin resistance. LVH in this group of patients could be due to the lack of the leptin attenuating effect on LV mass, similar to the occurrence of LVH in the hyperleptinemic, leptin-resistant db/db mice. It remains to be established whether pharmacological amelioration of leptin resistance will either prevent or, at least, attenuate LVH in rodent and human obesity.

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Response

Drs Tritos, Manning, and Danias raise the important issue of clinical relevance of left ventricular hypertrophy (LVH) in mice lacking the leptin receptor (db/db) or in mice lacking leptin itself (ob/ob), both of which exhibit morbid obesity. Human obesity is largely associated with leptin resistance and elevated leptin levels, and these investigators have demonstrated a positive correlation between leptin levels and LVH in obese subjects. Importantly, leptin levels are also elevated in chronic heart failure and chronic hypertension, suggesting the presence of leptin resistance in these disorders.

Indeed, we demonstrated reduction in LVH with leptin repletion in ob/ob mice, a model that can be considered analogous to reversing leptin resistance, as these mice have leptin receptors and presumably intact downstream signaling mechanisms. Interestingly, studies conducted in healthy individuals, free of cardiovascular disease and/or obesity, demonstrate inverse relationships between leptin levels and left ventricular mass index, suggesting that the primary impact of leptin is antihypertrophic when the signaling pathway is intact.

These studies considered together strongly support the notion that physiological leptin signaling has homeostatic cardiovascular activity. States of LVH—both obesity and other causes of heart failure—are states of leptin resistance and are therefore marked by elevated leptin levels. Thus, it will be essential to focus research efforts on the causes of leptin resistance and determination of whether heart failure and obesity have common leptin pathway signaling abnormalities. The totality of evidence further suggests that leptin-based interventions to reduce LVH will need to address the underlying causes of leptin resistance.

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