Interaction Between Exercise and Leptin in the Treatment of Obesity

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Recent data indicate that roughly 32% of the U.S. population is obese and an additional 34% is overweight (1). Considering the physical, psychological, and physiological complications associated with obesity, developing approaches to reduce these numbers is of critical importance. The identification of leptin as a hormonal link between energy stores and the brain inspired a renewed focus on the study of energy balance and contributed to the description of a neuronal network that mediates the metabolic regulation of feeding behavior, reproduction, glucose homeostasis, immune function, bone formation, lipid metabolism, etc. But for all its promise, much of the initial enthusiasm over leptin has waned with the realization that obese individuals respond rather poorly to leptin treatment and manifest a syndrome of leptin resistance. Although leptin may not be the anti-obesity treatment initially hoped for, there may yet be life to the leptin story. Just as progress has been made in defining and overcoming insulin resistance, considerable effort has focused on developing approaches to overcome leptin resistance. In this issue of *Diabetes*, Shapiro et al. (2) provide evidence that modest exercise synergizes with leptin treatment to markedly reduce body weight in individuals made obese by a high-fat diet, even though neither reduce body weight alone.

The importance of leptin in energy balance is illustrated by the extreme obese phenotype induced by leptin deficiency, and by the dramatic reduction in food intake and body weight that occurs upon treatment of this condition with leptin. While leptin levels are closely matched to body adiposity at steady state, negative energy balance produces a fall in leptin levels that is more rapid than the change in body adiposity. Preventing this fall is sufficient to attenuate many of the physiological events associated with negative energy balance, and it is widely agreed that leptin is a critical signal of weight loss. However, is the opposite also true? That is, does increased leptin serve as a signal of positive energy balance? Though the answer to this question is unclear, there is increasing evidence that enhancing leptin sensitivity produces a lean, obesity-resistant phenotype (3–6). These observations therefore suggest that leptin may indeed act to prevent weight gain, and that enhancing leptin sensitivity might be beneficial in the fight against obesity.

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The work by Shapiro et al. (2) builds upon previous experiments by the Scarpace group. This work demonstrates not only that prolonged leptin overexpression is ineffective at reducing body weight in obese rats, but also that chronic leptin treatment actually worsens diet-induced obesity (2,7). Far from providing a cure, chronic hyperleptinemia might actually contribute to obesity. But why would increased leptin levels make matters worse? First, it is important to note that the effect only occurs in animals on a high-fat diet, as those rats on a low-fat diet exhibited the expected leptin-induced reduction in body weight. Second, it appears that even a modest amount of exercise (in this case, wheel running) is sufficient to fully reverse this process and restore the response to exogenous leptin administration. This is perhaps the most profound observation in the study. Even though wheel running alone had no effect in obese rats, and despite the fact that leptin treatment made matters worse, the combination of the two produced a marked weight loss.

These unique outcomes leave us with a series of questions. Why does leptin treatment reduce body weight in chow-fed rats but paradoxically worsen obesity on a high-fat diet? Why does wheel running reduce weight in animals overexpressing leptin but have no effect in diet-induced obese controls, even though they are also hyperleptinemic and presumably leptin resistant? The authors logically focus on changes in leptin sensitivity as the underlying cause. In a previous study, the Scarpace lab demonstrated that when lean rats were subjected to chronic leptin overexpression, the initial decrease in body weight waned over time in association with a reduction in leptin sensitivity. When these rats were then placed on a high-fat diet, they displayed an enhanced diet-induced hyperphagia and weight gain (7). Together with the current work, these experiments indicate that by inducing leptin resistance, chronic hyperleptinemia attenuates the ability to resist diet-induced obesity.

It is likely that changes in leptin sensitivity may underlie the effects of wheel running as well. Previous experiments show that an acute bout of exercise improves leptin sensitivity (8), and in the current study markers of leptin action (pStat3 and Socs3) are increased in animals receiving the combination of leptin treatment and wheel running. Although phosphorylation of Stat3 is often used as a measure of leptin sensitivity, this is usually done in the context of acute administration. The current experiments measure steady-state levels, and in this scenario it is not clear how closely pStat3 levels correlate with leptin sensitivity. Furthermore, although high-fat diets and chronic leptin overexpression are proposed to induce leptin resistance, neither led to clear alterations in pStat3 and Socs3 levels compared with appropriate control rats in the current study. Thus, although some observations are consistent with a change in leptin sensitivity, the work falls short of providing definitive proof. It is also curious that

the effects of wheel running are only manifest in conjunction with exogenous leptin administration. If enhanced leptin sensitivity were the underlying mechanism, it would be expected that wheel running would also reduce body weight in the high fat–fed controls, since these animals are also hyperleptinemic and presumably leptin resistant. As noted by the authors, this outcome suggests there is something unique about exogenous leptin administration.

Developing approaches to resist or treat obesity is of critical importance to the U.S. health care industry. Shapiro et al. (2) highlight a synergistic interaction between leptin treatment and exercise and add to a growing list of experiments which indicate that enhancing leptin sensitivity reduces body weight and prevents diet-induced obesity. Leptin may yet yield an obesity treatment; in the meantime, perhaps I should go for a run.

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