Plasma Leptin and Exercise
Recent Findings

Matthew S. Hickey¹ and Dean J. Calsbeek²
1 Departments of Health and Exercise Science, Physiology, and Food Science and Human Nutrition, Colorado State University, Fort Collins, Colorado, USA
2 Department of Physiology, Colorado State University, Fort Collins, Colorado, USA

Abstract

The cloning of murine and human obese genes in 1994, and the subsequent identification that the product of the obese gene, leptin, is secreted from adipose tissue, stimulated a tremendous amount of interdisciplinary interest in adipose tissue endocrinology and the potential role of this tissue in the regulation of energy balance. Exercise, with concomitant changes in fuel flux, systemic hormone levels and energy expenditure, may contribute to the regulation of plasma leptin levels and presumably, leptin action. The initial work characterising the leptin-exercise relationship was equivocal. Cross-sectional studies provided some mixed evidence regarding the relationship between aerobic capacity or habitual physical activity and plasma leptin.

In contrast, studies on acute bouts of exercise and exercise training interventions have, with few exceptions, suggested that exercise does not alter systemic leptin independent of changes in fat mass. In general, these studies did not carefully control for energy balance, and sampled only a single fasting plasma leptin level. Two recent studies utilising experimental designs in which energy balance was controlled and 24-hour profiles of plasma leptin were determined have provided the most compelling evidence to date of the interaction between exercise, energy balance and systemic leptin in humans. These studies provide a clear explanation for the apparent lack of an acute effect of exercise on systemic leptin and underscore the importance of clearly defining the balance between energy intake and energy expenditure when studying the physiology of leptin. The aim of this brief review is to provide an overview of the interaction between energy expenditure during physical activity and systemic leptin level. Special emphasis will be placed on those studies in which energy intake/balance was carefully controlled.

1. Background

Leptin circulates as a 16kDa protein, the product of the obese gene¹. The cloning of the obese gene in 1994 by Friedman’s group¹ was significant in 2 respects: first, it highlighted a rich chapter in the history of physiology by providing evidence that the lipostatic factor postulated from the work of Kennedy² nearly 40 years earlier had been identified (although this should not be taken to mean we have a complete understanding of adipose tissue as an endocrine organ); second, it provided a powerful impetus to interdisciplinary research on the biology of leptin, and more importantly, the integrative biology of energy balance. This intense interest is best evidenced by the nearly 3000 peer-reviewed
Seven years of intense study of leptin expression, secretion and action have led to the conclusion that, contrary to the initial impression, leptin is not simply an ‘anti-obesity’ hormone, nor does it always reflect adipose tissue mass. In fact, it has been suggested that leptin is primarily an anti-starvation hormone. The response of systemic leptin to partial or total energy restriction is a rapid and profound decrease, implying that energy restriction is a potent signal to reduce leptin secretion. Leptin appears to be involved in regulating the physiological adjustments to starvation, which defend the organism from excess energy expenditure in the face of limited availability of energy intake. From a survival standpoint, regulating this response is likely to be much more relevant than defending against excess accumulation of body fat (at least until recently).

Interestingly, the increased scrutiny of adipose tissue has led to a much more comprehensive appreciation of the complexity of this tissue, and the wide variety of secreted products that are derived from white adipocytes.

2. Biology of Leptin

Leptin is a peptide of 146 amino acids that circulates as a 16kDa monomer in both bound and free forms. Leptin is expressed in and secreted primarily from white adipose tissue, although recent work suggests other tissues, including skeletal muscle, stomach, brain and the placenta, may also be sites of leptin production. The extent to which these other tissues contribute to systemic leptin levels is not clear.

Leptin receptors share homology with the class I cytokine receptor family and at least one leptin receptor isoform signals intracellularly through the JAK-STAT (Janus kinase–signal transducers and activators of transcription) pathway. There are a number of splice variants of the leptin receptor, with tissue-specific expression patterns. Leptin receptors are expressed in a variety of tissues, including the hypothalamus, choroid plexus, β-cells of the pancreas, adipose tissue, liver, kidney, jejunum, lung, adrenal medulla, ovaries, testes, placenta, heart and skeletal muscle. The long form of the leptin receptor (OB-Rb) is preferentially expressed in the hypothalamus, and is known to activate the JAK-STAT pathway. Obese diabetic (db/db) mice, which have a mutation resulting in the production of a truncated form of OB-Rb are unresponsive to leptin, confirming that OB-Rb is required for the action of leptin on food intake and energy expenditure. The predominant short form of the receptor, OB-Ra, is expressed in a number of peripheral tissues and in the choroid plexus. OB-Re, another short form of the receptor, is thought to be a soluble form of the receptor and may act as a binding protein.

Leptin action at target tissues can include both changes in gene expression and intermediary metabolism (fig. 1). In humans, the systemic leptin level is proportional to body fat mass, which has led to the suggestion of a ‘leptin resistant’ state in human obesity. Like several other hormones, plasma leptin exhibits a clear circadian rhythm, with the zenith occurring near midnight, and the nadir in early to mid-morning (fig. 2). Schoeller and colleagues have provided evidence that the 24-hour leptin rhythm is entrained to meal timing, as evidenced by a phase shift that corresponds to a shift in energy intake patterns. The regulation of leptin secretion is complex, and is thought to include the sympathetic nervous system, nutrients (glucose and fatty acids), insulin and glucocorticoids. Evidence for a role of sex steroids is less clear.

Recent work from a number of laboratories has provided evidence that intracellular products of glucose metabolism in the hexosamine pathway may act as specific regulators of leptin expression in adipose tissue (see fig. 1 for an overview).

Interestingly, despite the rather remarkable pace of research on the cell biology of leptin, there have been less than 3 dozen studies specifically addressing exercise-leptin interactions in humans. While space limitations preclude a detailed discussion of all the work in this area, including the work on paediatric populations, research on leptin and
exercise has in general taken 3 traditional approaches: cross-sectional studies, short term (single bout) exercise studies and exercise training. In cross-sectional studies, the log of plasma leptin has been reported to be negatively related to ‘fitness’ [maximal treadmill time, (maximal oxygen uptake: \(V\text{O}_{2}\text{max}\))][26-28] but this relationship is generally not independent of adiposity. In contrast, studies with discrete groups of athletes vs sedentary controls have suggested an effect of long term exercise training that could not be entirely accounted for by differences in fat mass alone.[18,29] There is considerable emerging evidence that leptin may be intimately involved in regulation of reproductive function in women athletes.[18,29,30] The involvement of leptin in the reproductive axis is a major interest area for future research.

Short term exercise studies generally showed little or no effect on plasma leptin,[31-37] unless the energy expenditure was profound.[38,39] However, it should be noted that several recent studies have reported delayed changes in plasma leptin several hours (2 to 48 hours) after a single bout of exercise.[40-43] The physiologic significance of the delayed drop in plasma leptin is unclear.

Exercise training studies in general have suggested that changes in plasma leptin are dependent upon concomitant reductions in body mass.[44-52] Exceptions to this include work from our group suggesting that plasma leptin may be reduced in exercise-trained females despite stable fat mass,[53] a study from Pasman et al.[54] that suggested that an independent effect of exercise on plasma leptin in males is detectable after 10 months of training, and a study by Okazaki et al.[46] that reported reductions in plasma leptin independent of changes in fat mass in sedentary Japanese women following a 12-week diet plus exercise intervention. Given the foregoing, one might be justifiably frustrated in attempting to discern a clear interaction between exercise and systemic leptin.

3. Exercise and Leptin 24-Hour Rhythm

Two recent studies have highlighted the care that is necessary in investigating leptin-exercise interactions.[19,20] Because leptin is acutely sensitive
negative energy balance, it is important to design studies which can distinguish the effects of exercise per se from any attendant change in energy balance. Moreover, leptin, like many other hormones, exhibits a clear diurnal rhythm. The vast majority of research on exercise to date has incorporated only a single fasting sample and drawn conclusions from this ‘snapshot’ of the diurnal pattern. The characterisation of 24-hour plasma leptin profiles provides a much more informative (and representative) view of the dynamic effects of exercise on leptin.

Van Aggel-Leijssen et al. studied 8 healthy, lean (14.5% fat), sedentary males. Individuals were studied under 4 conditions: (i) no exercise-energy balance; (ii) exercise-energy balance (2 hours at 50% VO₂max, equivalent to ≈800 kcal); (iii) exercise-negative energy balance (energy deficit of ≈800 kcal); and (iv) exercise-positive energy balance (energy surplus of ≈833 kcal). The exercise-energy balance condition resulted in a 20% reduction in the weighted average 24-hour leptin level. In contrast, the exercise-negative energy balance condition did not alter 24-hour leptin levels.

Exercise-positive energy balance was without effect on average 24-hour leptin level, but did increase the amplitude of the 24-hour leptin curve by 2-fold compared with the exercise-energy balance condition. Importantly, no treatment altered baseline (0900h) plasma leptin level in this study, reinforcing the view that the earlier studies were correct in this regard, but likely missed effects of the exercise bout on 24-hour leptin profiles. Finally, it should be noted that stepwise regression analysis suggested that 98% of the variance in 24-hour plasma leptin could be explained by the combination of fasting plasma nonesterified fatty acids and glucose. While this may be taken as indirect support of the concept that leptin expression is regulated by some aspect of fuel flux in adipose tissue, the cellular mechanisms of such a regulatory pathway(s) are not fully understood.

Hilton and Loucks incorporated a similar design to study the influence of energy availability on 24 average leptin levels. A total of 16 healthy, eumenorrhoeic women were studied. Energy availability was operationally defined in this study as the difference between dietary energy intake and controlled exercise energy expenditure (energy intake – exercise energy expenditure = energy availability). Put another way, energy availability is the amount of dietary energy ‘left over’ for other biological processes after exercise has consumed a given amount of the daily energy budget.

Individuals were assigned to nonexercise and exercise groups and studied twice. The nonexercise group completed: (i) balanced energy availability (both energy intake and energy availability = 45 kcal/kg lean body mass (LBM)/day, which was equivalent to a habitual energy intake of ≈2000 kcal/day in these individuals); and (ii) low energy availability (energy intake and energy availability = 10 kcal/kg LBM/day, equivalent to 78% energy restriction, or ≈430 kcal/day) trials. Energy availability in the exercise group was matched to the sedentary individuals (i.e. energy availability = 45 kcal/kg LBM/day in the balanced trial and 10 kcal/kg LBM/day in the low energy availability trial). The matching was achieved by fixing exercise energy expenditure at 30 kcal/kg LBM/day in both exercise trials (≈1300 kcal/day) and varying energy intake accordingly. Importantly, each diet or diet plus exercise treatment lasted 4 days.
When energy availability was matched between groups, exercise was without effect on either the 24-hour mean or the amplitude of the diurnal leptin rhythm. In contrast, irrespective of the magnitude of exercise energy expenditure, low energy availability reduced both the 24-hour mean (−72%, −53%) and amplitude (−85%, −58%) of the diurnal leptin rhythm (no exercise and exercise groups, respectively). It is important to note that the reductions in leptin levels in the exercise group occurred during a 4-day period when total energy intake in this group was \approx 1700\ kcal. Thus, an important observation from this study is that leptin responds not to energy intake (or expenditure) per se, but acts as a sensor of the difference between energy intake and expenditure.\[20\]

The mechanism by which leptin 'senses' differences between energy intake and expenditure is not clearly understood at this time, although Hilton and Loucks\[20\] suggested that leptin may in fact be responding to changes in carbohydrate availability. Wang et al.\[7\] and McClain et al.\[22\] have recently provided evidence that intracellular products of glucose metabolism are involved in regulating leptin secretion, providing a potential mechanism to explain the observations of Hilton and Loucks.\[20\] If further work confirms that a product(s) of glucose metabolism acts as a regulator of leptin secretion, then we will be faced with the profoundly interesting situation in which a hormone derived from fat cells, thought to act in part as a 'lipostat', may be more closely regulated by glucostatic factors.

There are key differences in the experimental design of the studies by van Aggel-Leijssen et al.\[19\] and Hilton and Loucks\[20\] that should be noted. The low energy availability condition of Hilton and Loucks\[20\] represented a 78% reduction in habitual energy intake for a period of 4 days. While there is no directly comparable condition in the study of van Aggel-Leijssen et al.,\[19\] the exercise-negative energy balance (28% negative energy for 24 hours) condition in this study was without effect on 24-hour mean and amplitude of the diurnal leptin rhythm. As Hilton and Loucks\[20\] suggest, this would imply that there is a threshold reduction in energy availability that must be reached to alter the dynamics of the diurnal rhythm of leptin. Alternatively, there may be a gender difference in the sensitivity of leptin to changes in energy availability. It is also possible that the moderate negative energy balance of −28% would require more than 24 hours to impact on the leptin rhythm. Clearly, more research needs to be conducted regarding the biology of leptin; a summary of selected future research questions which need to be addressed is presented in table I.

4. Conclusion

The work of van Aggel-Leijssen et al.\[19\] and Hilton and Loucks\[20\] are both elegant and complex. They are informative in that they provide evidence of the limitation of studies using a single fasting blood sample to assess diet/exercise effects on systemic leptin. Both studies also make it clear that careful consideration of energy balance is warranted when studying the biology of leptin. Because of the differences in gender and design between these studies, generalisations about the effect of exercise on leptin remain elusive. However, should the work of Hilton and Loucks\[20\] be confirmed (particularly in males), it will provide additional support for the hypothesis that leptin responds not...
to energy intake or exercise energy expenditure alone, but to the balance between the two.

The consideration that leptin may respond not to isolated components of energy balance (i.e. intake or expenditure alone) is perhaps not surprising. The ability of an organism to ‘sense’ both the energy expenditure and energy requirements is essential to appropriately respond to both energy deficits and energy surplus. The maintenance of an appropriate energy budget on a day-to-day basis, when energy expended in physical activity, total energy expenditure, and energy intake may all be changing, is obviously an essential component of both survival and viability. However, it is not clear at present what, if any, clinical relevance exercise-induced alterations in the 24-hour leptin rhythm may have.

Much more work needs to be done regarding how exercise impacts upon leptin secretion, clearance and most importantly, leptin action at target tissues. Our understanding of the integrative biology of leptin has progressed considerably in the past 6 years. These continued research efforts have primarily served to highlight the complexity of the energy balance regulatory systems.

Acknowledgements

Funding support came from United States Department of Agriculture (USDA) grant #COL00762.

References

13. Harris RBS. Leptin – much more than a satiety signal. Annu Rev Nutr 2000; 20: 45-75
Effect of Exercise on Plasma Leptin

Correspondence and offprints: Matthew S. Hickey, Department of Health and Exercise Science, 218E Moby Complex, Colorado State University, Fort Collins, CO 80523, USA. E-mail: hickey@cahs.colostate.edu

© Adis International Limited. All rights reserved.

Sports Med 2001; 31 (8)

44. Kohrt WM, Landi M, Bierge Jr SJ. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older women. J Clin Endocrinol Metab 1996; 81 (11): 3980-5