Physical Activity and Hormonal Regulation of Appetite: Sex Differences and Weight Control

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Abstract

Physical activity is an important contributor to regulation of energy balance and body composition. In this article, we separate the impact of exercise from the confounding influence of energy imbalance and highlight sex differences in hormonal and appetite responses to physical activity. The evolving story may influence our thinking regarding the use of physical activity to manage body composition.

Keywords:

exercise; energy intake; body fat; ghrelin,; insulin; leptin; PYY

INTRODUCTION

Obesity is a global epidemic and is associated with an increased risk for type 2 diabetes and cardiovascular disease ([20, 24]). Restricting energy intake, the most obvious strategy to reduce body fat and lower risk for obesity-related disease, is generally unsuccessful. More than 90% of obese individuals regain lost body fat within 2 yr ([31]). An alternative to restricting energy intake is raising total energy expenditure by increasing physical activity. Regular physical activity is widely recognized as playing a large role in the regulation of energy balance and body composition. Interventions based on physical activity alone (no restriction of energy intake) tend to be ineffective in causing appreciable body fat loss ([7]), with the best results achieved through a combination of physical activity and energy restriction. However, several recent studies show that exposure to exercise training programs with *ad libitum* diet does cause loss of body fat in men but are far less effective in women ([12, 26]). These results imply that the differential effects of physical activity on weight loss likely involve changes in appetite and/or satiety, which are mediated, at least partly, by circulating hormones integral to the regulation of energy balance (*e.g.,* acylated ghrelin, insulin, leptin). Our recent work, showing that the hormonal and appetite responses to exercise are strongly influenced by energy balance in men, but much less so in women, suggested to us that physical activity affects the energy intake side of the energy balance equation, and this effect differs by sex. This article will focus on recent data centered on how physical activity impacts the hormonal responses that regulate appetite and energy intake. We highlight sex differences because sex-specific hormonal, metabolic, and appetite responses to physical activity may influence the application of physical activity to weight management.

Description of Energy Balance and Energy-Regulating Hormones

Energy status is defined as the relationship between dietary energy intake (EI) and energy expenditure (EE), typically measured over 24-h periods. Energy status is considered in "balance" when EI = EE, in deficit when EI < EE and in surplus when EI > EE. Energy deficits or surpluses can be incurred by

manipulating EI (*i.e.,* underfeeding or overfeeding), EE (*i.e.,* adding or subtracting physical activity) or both.

Energy balance and ultimately, body fat, is regulated by a negative feedback system in which changes in body energy content (*i.e.,* body fat) are reflected by changes in appetite, energy intake, and energy expenditure. Keys to the regulation of these systems are hormones with energy-regulating properties (*e.g.,* acylated ghrelin, leptin, insulin) that sense changes in energy balance and convey information to central processing centers in the brain. There, increased or reduced secretion of neurotransmitters (*e.g.,* neuropeptide Y, agouti-related protein) within the arcuate nucleus of the hypothalamus and the hindbrain stimulate or suppress energy intake and energy expenditure. We are cognizant that these hormones impact other physiological pathways, such as reproductive function and partitioning of blood flow, but for the purpose of this review article, we will refer to these hormones with energy-regulating properties as "energy-regulating hormones."

Energy-regulating hormones are commonly classified into two categories, episodic (short-term) and tonic (longer-term) signals. Episodic signals regulate meal initiation and termination and so determine frequency of meals and meal size. Ghrelin, particularly the acylated form that binds to receptors in the hypothalamus, hindbrain, and other tissue, is widely recognized as the main episodic signal to stimulate energy intake. Peripheral infusion of ghrelin raises circulating ghrelin concentrations and, along with the cannabinoids, are the only compounds known to directly stimulate energy intake in animals and humans ([34, 35]). Emerging evidence also indicates that peptide tyrosine-tyrosine (PYY) plays a role in meal size and termination. Peripheral infusion of PYY_{3-36}, the most common and potent form of PYY, suppresses subsequent food intake in both animals ([2]) and humans ([1]). In addition, PYY-knockout mice are hyperphagic and have higher body fat than the controls, which indicates that PYY may help regulate long-term body weight ([3]).

Tonic signals, such as leptin and insulin, are more likely to regulate overall energy balance and body fat over days or weeks rather than meal to meal. In animals, higher circulating concentrations of these

hormones suppress energy intake and stimulate energy expenditure ([13, 18]). Paradoxically, obese individuals usually have higher concentrations of circulating leptin and insulin, suggesting that they may be "resistant" to the effects of these hormones to suppress energy intake. Recently, investigators showed that lower concentrations of leptin and insulin stimulate appetite and energy intake and suppress energy expenditure ([4, 33]). These data indicate that a major role of tonic hormones may be to oppose continued energy deficit and maintain body fat. It is possible that the relationship between leptin/insulin concentrations and energy intake is the familiar "inverted U" in which both low and very high concentrations of leptin/insulin stimulate food intake, but moderate circulating levels have a suppressive effect.

Sex hormones, particularly estradiol, have a clear impact on the regulation of energy balance, at least in animals. For example, estrogen deficiency resulted in higher energy intake and increased body weight in ovariectomized rodents ([11]). In contrast, progesterone and testosterone concentrations seem to have little, if any, impact on food intake. In women, energy intake may vary across the menstrual cycle ([10]). In general, women tend to eat more in the luteal phase compared with the follicular phase of the menstrual cycle. These data also indicate the importance of accounting for the potentially confounding impact of menstrual cycle phase when directly comparing men and women.

Effects of Energy Status on Energy-Regulating Hormones

Changes in energy status (*i.e.,* deficit, balance, surplus) have a profound impact on the hormonal responses that modulate appetite, energy intake, and energy expenditure. Also, it is possible that energy status ([22]) may influence sensitivity to ghrelin (*e.g.,* energy deficit = increased ghrelin sensitivity, energy surplus = ghrelin resistance). Energy deficit increases appetite, raises circulating concentrations of acylated ghrelin, and lowers blood concentrations of leptin and insulin. These responses are expected, based on the known and purported actions of the hormones, to reverse the energy deficit and maintain (or even restore) body energy supplies. Although the hormonal responses to energy deficit have been studied, the effects of energy surplus are less characterized. We showed ([15, 16]) that 3 d of energy surplus

(overfeeding by +750 kcal·d^{-1}), raised fasting leptin and insulin concentrations in the blood but the suppression of ghrelin may depend on physiological state (fasted vs glucose stimulated). Ravussin *et al*. ([27]) and Robertson *et al*. ([28]) both found no change in fasting ghrelin concentrations after long-term overfeeding. However, Robertson *et al*. ([28]) did observe a steady decline in the ghrelin area under the curve in response to a high-fat meal after 3 wk of overfeeding. In contrast, we found that the ghrelin response to ingestion of glucose was unaffected after 3 d of overfeeding (Fig. 1; [16]). The likely differences may hinge on the duration of overfeeding (3 wk vs 3 d) and/or the macronutrient used to alter ghrelin concentrations (fat vs glucose). However, our data suggest that a mechanism to lower ghrelin concentrations is not obvious after 3 d of overfeeding.

Effects of Exercise on Energy-Regulating Hormones

Physical activity, at least in the form of structured exercise, alters hormones that modulate energy balance. A critical issue for interpretation of the exercise data is teasing apart the effects of exercise *per se* from the potentially confounding influence of an accompanying energy deficit. In research studies, the energy expended during exercise is rarely replaced by increasing dietary energy. As a result, outcomes may be attributed to exercise when they are actually being driven by energy deficit. For example, energy deficit raises circulating concentrations of acylated ghrelin and lowers insulin and leptin, with the net effect to stimulate appetite and raise energy intake.

To separate the independent effects of exercise from the impact of energy imbalance, it is necessary to assess outcomes in both energy-balanced (dietary energy intake raised to match higher energy expenditure) and energy-deficient (energy intake not raised to match energy expenditure) conditions. In one study from our laboratory ([5]), two matched groups of overweight, insulin-resistant adults completed six daily bouts of exercise in energy deficit (dietary energy not added to compensate for higher energy expenditure) or energy balance (dietary energy added to baseline diet) conditions. We found that, compared with baseline, exercise with concurrent energy deficit lowered blood concentrations of leptin and insulin (both of which would be expected to stimulate energy intake). However, restoring energy

balance completely abolished this effect with no change in either leptin or insulin concentrations. These results suggested that energy deficit, not exercise *per se*, was the major regulator of the hormonal responses observed when previously sedentary individuals began a regular program of exercise training.

In contrast, a separate study from our laboratory suggested otherwise ([15, 16]). Circulating concentrations of energy regulating hormones were measured in nine healthy, habitually active individuals after a no-exercise baseline condition, 3 d of overfeeding (no structured exercise), and 1 d of overfeeding plus 60 min of moderate-vigorous exercise. Energy intake and expenditure were rigidly controlled, and the subjects were in the same relative energy surplus (+750 kcal·d^{-1}) after the overfeeding alone and overfeeding plus exercise conditions. Fasting concentrations of leptin, insulin, and ghrelin were not responsive to exercise when performed against a background of energy surplus. In contrast, there was greater suppression of circulating ghrelin after oral consumption of glucose (suggesting less stimulation of food intake) by combining exercise and energy surplus (Fig. 1; [16]). A similar pattern was also reported by others, who showed that aerobic exercise (with energy balance maintained for a short period), suppressed ghrelin concentrations compared with a no-exercise condition in habitually active men ([9]). These data suggested that exercise alters energy-regulating hormones even when there is no accompanying energy deficit. These results are in disagreement with the previous study from our laboratory ([5]) showing that energy deficit, and not exercise alone, drives changes in energy-regulating hormones. Differences in the subject characteristics (overweight, sedentary, and insulin resistant in Black *et al*. ([5]) vs relatively lean, active, and insulin sensitive in Hagobian *et al*. [16]), exercise protocols (six consecutive days of exercise in Black *et al*. ([5]) vs one bout of exercise in Hagobian *et al*. [16]), and energy status (deficit vs balance in Black *et al*. ([5]), surplus vs balance in Hagobian *et al*. [16]) could all play a role in explaining the dissonance between the two studies from our laboratory.

Emerging evidence indicates that some forms of physical activity may alter plasma concentrations of PYY in a direction expected to suppress energy intake. Martins *et al*. ([23]) showed that PYY was elevated during moderate intensity aerobic exercise. Similarly, Broom *et*

al. ([8]) found that aerobic exercise elevated PYY concentrations, but resistance exercise (weight lifting) had no impact on concentrations of PYY. These data are consistent with the paradigm that moderate to high intensity aerobic exercise transiently suppresses energy intake and appetite.

To directly address the "exercise versus energy status" question in a systematic way, we designed a study to determine whether the effects of exercise on hormonal and appetite responses that regulate energy metabolism were independent of energy status. A second goal of the study was to gain insight into another controversial issue with both basic science and public health relevance - the strong data indicating that, upon the initiation of aerobic exercise training, men lose more body fat than women.

Sex Differences in Energy-Regulating Hormones

In general, using regular physical activity as a tool to induce body fat loss is more effective in men than in women ([12, 25]). Donnelly *et al.* ([12]) and Potteiger *et al.* ([26]) reported that supervised aerobic exercise for 16 months lowered body fat in men who ate *ad libitum*, but there were no changes in body fat in women. These data are corroborated by similar studies in animals. Oscai *et al*. ([25]) observed that female rats swimming 6 $h \cdot d^{-1}$ for 6 wk gained weight at the same rate as sedentary controls, whereas male rats swimming for 6 wk weighed less than their sedentary counterparts. These data suggest that in response to aerobic exercise training, women more accurately match energy intake with energy expenditure and thus preserve body fat. In contrast, men do not sufficiently increase energy intake to balance the new higher energy expenditure and therefore lose body fat.

Sex differences in the efficacy of exercise to induce body fat loss may be mediated by male-female differences in the hormonal response. Sex-based differences in the hormonal response may be manifested in changes to appetite, energy intake, and energy expenditure that more effectively stimulate appetite and energy intake (and possibly suppress energy expenditure) in women than in men. To specifically address both the "exercise versus energy status" and the "sex differences in energy-regulating hormones"

questions, we assessed the effects of exercise on energy-regulating hormones in previously sedentary, overweight/obese men and women ([17]). Energy-regulating hormones were measured in the fasted state and during a meal tolerance test in three distinct conditions using a counterbalanced, cross-over study design: no-exercise baseline, after four daily bouts of exercise with dietary energy added to maintain energy balance, and after four daily bouts of exercise without dietary energy added (energy deficit). To control for the confounding influence of sex hormones, all women were tested in the early follicular phase of the menstrual cycle.

We observed clear sex differences in the way that exercise altered energy-regulating hormones and appetite. In response to exercise without energy added back to the diet, women had higher concentrations of acylated ghrelin (Fig. 2) and lower concentrations of insulin (Fig. 3), both of which would be expected to stimulate energy intake. When dietary energy intake was increased to maintain energy balance, the pattern of response in acylated ghrelin and insulin concentrations was attenuated but persisted, implying some independent effects of exercise. In men, however, exercise had a more modest impact on these hormones. Acylated ghrelin concentrations did not change in men regardless of energy status (Fig. 2). Insulin concentrations were lower in the energy deficit condition (Fig. 3), but this effect was completely absent when dietary energy was increased to restore energy balance.

In the few other studies in which sex differences in energy-regulating hormones has been assessed, the results are consistent with ours. Gayle *et al*. ([14]) showed that ghrelin concentrations and *ad libitum* food intake were higher after a 12-h fast in female rats compared with male rats. An exercise-induced energy deficit sufficient to cause weight loss increased ghrelin concentrations in women ([21]), whereas men had no change in ghrelin concentrations ([27]). In the one other study designed to directly assess sex differences in multiple energy-regulating hormones, Hickey *et al*. ([19]) found lower insulin and leptin concentrations after 12 wk of exercise in women, but there was no change in men. Taken together, these data suggest that exercise induces larger changes to energy-regulating hormones in women than in men. The direction of the changes is consistent with the hypothesis that appetite will be stimulated more in women than in men.

If these changes in hormones are reflected in parallel changes to appetite and, more importantly, to actual food intake, it should be no surprise that women more effectively "defend" body fat in response to increased physical activity with *ad libitum* food intake.

In women, better matching of energy intake to energy expenditure in response to physical activity may be driven by the critical relationship between energy balance and reproductive success. For example, energy deficiency suppresses ovulatory cycles, inhibits gonadotropin-releasing hormone secretion, reduces pulsatility of luteinizing hormone, and stops copulatory behavior ([32]). In men, however, energy deficiency seems to have no major impact on reproductive success. Therefore, in women, higher acylated ghrelin and lower insulin/leptin concentrations in response to physical activity may be a mechanism to oppose energy deficit, defend body fat stores, and preserve reproduction function. It is likely that the relationships between insulin, ghrelin, and leptin, on reproductive function are strongly interrelated to their roles as indicators of energy availability, rather than as primary reproductive signals ([32]).

Does Exercise Alter Appetite and Actual Food Intake?

In addition to sex differences in blood acylated ghrelin and insulin concentrations, we also found male-female differences in appetite response to the initiation of exercise training ([17]). In men, responses to appetite questionnaires indicated less desire to eat, less perceived hunger, and lower scores on a "how much food can you eat" question when energy intake was raised to offset the extra energy expended and maintain energy balance. In women, however, appetite responses were not responsive to the increased dietary energy. These data are in agreement with some ([9]) but not other ([29, 30]) previous studies focused on how exercise (1-9 bouts) impacts appetite and food intake. The differences in appetite responses in these studies may hinge on whether energy intake was controlled or allowed to vary. In our study and in Broom *et al*. ([9]), energy intake was controlled by feeding the subjects weighed, measured meals throughout the intervention. In contrast, others ([29, 30]) allowed the subjects to eat *ad libitum* and assessed food intake through a diet recall. The advantages of *ad libitum* eating (get an actual measure of "free-living" energy intake) have to be balanced with the known difficulties with reconciling self-reported data using dietary

recall with actual energy intake. In our study, knowing exactly what the subjects consumed on a daily basis allows us to conclude that there are potentially important sex differences in how physical activity affects perceived appetite.

Although we found that exercise altered the hormonal and appetite responses in a sex-specific manner, there was imperfect concordance between the two seemingly related measures. For example, the hormone data suggest that exercise should increase food intake in women but have no effects on food intake in men. In contrast, our appetite data suggest exercise would have no effects on food intake in women and decrease food intake in men. The disconnection is supported by a recent study showing that the energy-regulating hormones and appetite respond to different physiological/metabolic signals ([6]). Borer *et al*. ([6]) suggest that appetite is influenced by recent energy intake (*i.e.,* food ingestion through the mouth), whereas circulating concentrations of energy-regulating hormones are responding to changes in energy status (deficit, balance, and surplus).

The key question that remains unanswered is whether sex differences in energy-regulating hormones and/or perceived appetite are reflected by differences in *ad libitum* food intake. To our knowledge, all three relevant variables (*i.e.,* hormones, appetite, and food intake) have not been systematically assessed in a single study. Because, by design, we controlled energy intake and energy expenditure (both independent variables), we were unable to determine whether sex differences in the hormonal and appetite responses would translate to differences in actual food intake. One study ([30]) showed that women increased *ad libitum* food intake to partially compensate for the new higher energy expenditure due to exercise, but there was no change in perceived appetite (hormonal response was not measured). In contrast, men did not increase *ad libitum* food intake ([29]). These results are supported by a study showing that after a 12-h fast, female rats had higher ghrelin concentrations and higher *ad libitum* overnight food intake compared with male rats ([14]). Although much more work needs to be done, the results to date suggest that sex differences in the way regular physical activity impacts energy-regulating hormones and

appetite may lead to different patterns of food intake and, ultimately, different effects on body fat loss (Fig. 4).

CONCLUSIONS AND FUTURE DIRECTIONS

It is generally accepted that regular physical activity, with no deliberate dietary changes, results in greater body fat loss in men compared with women. Our recent work, and that of others, led us to the view that male-female differences in the hormonal and appetite responses to physical activity may alter the role played by physical activity in the regulation of body weight. These sex-based differences have implications for our understanding of both basic science (*e.g.,* what signaling pathways underlie the sex differences in whole-body metabolism and what tissues are they located in?) and practical application (*e.g.,* diet/exercise recommendations for the general public). Many of the basic science questions will be addressable in animals genetically modified to underexpress or overexpress particular pathways. Based on those results, researchers will be able to design clever studies in humans to understand the applicability to regulation of human energy expenditure. Ultimately, the objective is to understand the complex web of interrelated signals sufficiently to address important public health questions. Are sex differences in energy-regulating hormones and appetite so meaningful that they lead to sex-specific physical activity recommendations? Is it necessary for most women (but fewer men) to increase energy expenditure and restrict energy intake to lose body fat and/or maintain their ideal body weight/composition? As usual, answering these questions requires a series of research studies at several different "scales" (*e.g.,* cell, organ systems, whole organism, population).

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Figures

Figure 1

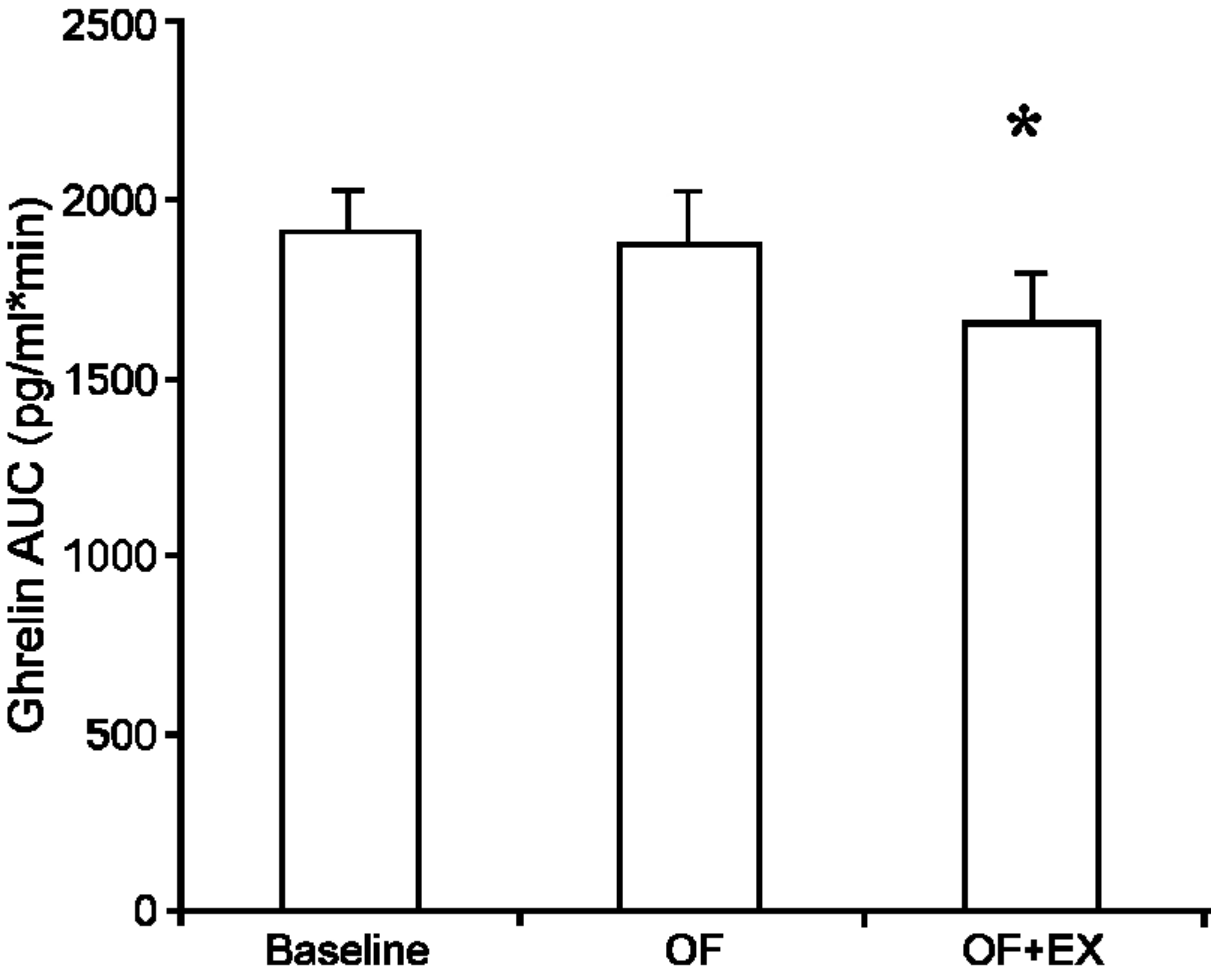
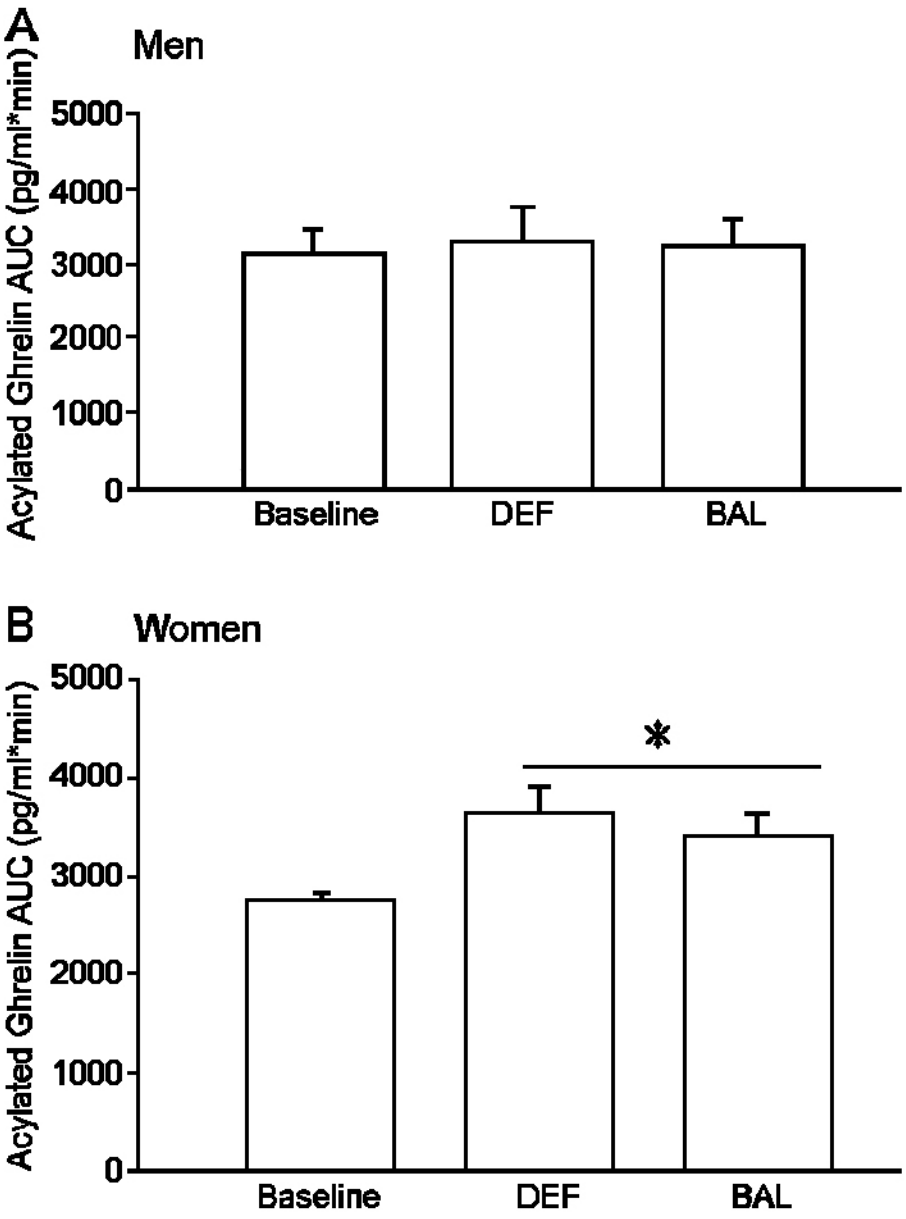


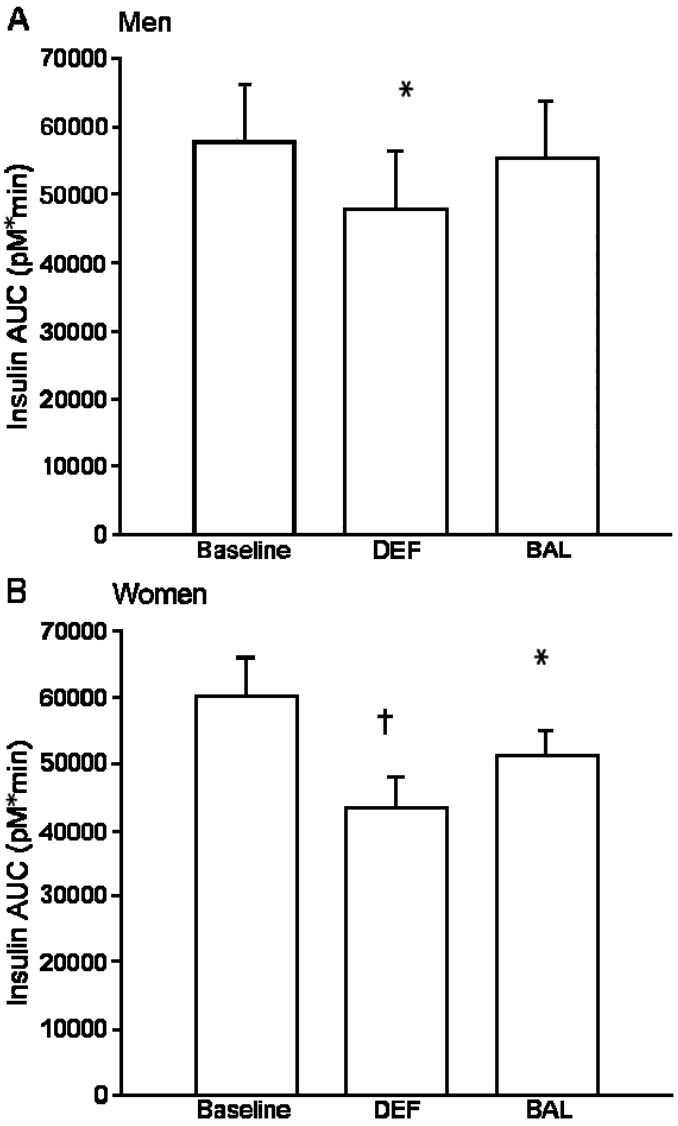
Figure 1. Plasma ghrelin area under the curve (AUC) during a 60-min oral glucose challenge the morning after baseline, 3 d of overfeeding (OF), and 1 d of overfeeding plus 60 min of aerobic exercise (OF+EX). Aerobic exercise significantly lowered plasma ghrelin concentrations independent of changes in energy balance. *Significantly different than baseline and OF. Pg/mL = picograms ghrelin per milliliter plasma. (Reprinted from Hagobian TA, Sharoff CG, Braun B. Effects of short-term exercise and energy surplus on hormones related to regulation of energy balance. Metabolism. 2008; 57(3):393-8 Copyright © 2008 Elsevier. Used with permission.)

Figure 2



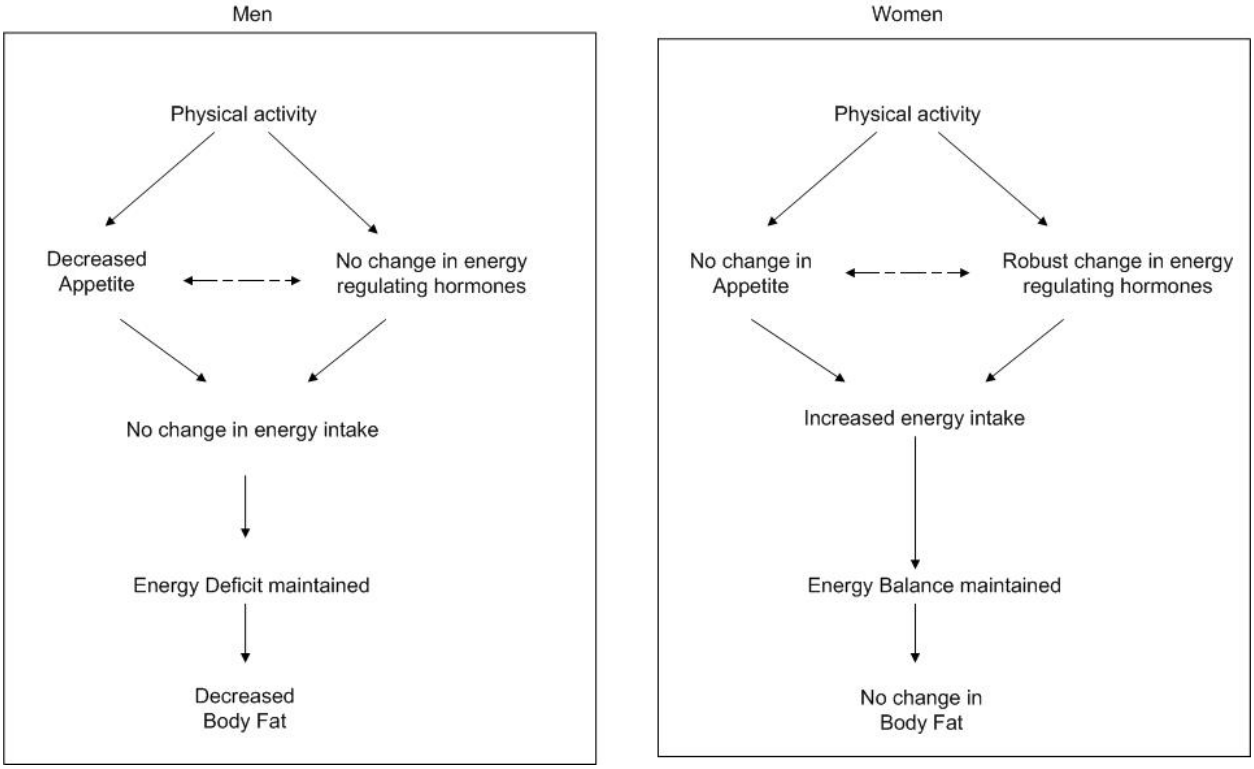
Plasma acylated ghrelin area under the curve (AUC) during a 2-h meal tolerance test after baseline (no exercise), exercise in energy deficit (DEF), and exercise in energy balance (BAL) conditions in overweight/obese men (A) and women (B). Women had a higher acylated ghrelin response (indicating more stimuli to eat) after both exercise conditions, and the change from baseline was significantly higher than that in men. *Significantly higher than baseline. . [Adapted from Hagobian TA, Sharoff CG, Stephens BR, et al. Effects of exercise on energy-regulating hormones and appetite in men and women. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2009; 296(2):R233-42. Copyright © 2009 The American Physiological Society. Used with permission.]

Figure 3



Plasma insulin area under the curve (AUC) during a 2-h meal tolerance test after baseline (no exercise), exercise in energy deficit (DEF), and exercise in energy balance (BAL) conditions in overweight/obese men (A) and women (B). Women had a lower insulin response (indicating more stimuli to eat) after both exercise conditions. *Significantly lower than baseline. †Significantly lower than baseline and BAL. pM = picomoles/liter plasma. [Adapted from Hagobian TA, Sharoff CG, Stephens BR, et al. Effects of exercise on energy-regulating hormones and appetite in men and women. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2009; 296(2):R233-42. Copyright © 2009 The American Physiological Society. Used with permission.]

Figure 4



Hypothetical model of how physical activity impacts hormonal and appetite regulation of energy balance in men and in women.

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