MINIREVIEW

Exercise and Humoral Mediators of Peripheral Energy Balance: Ghrelin and Adiponectin

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Ghrelin and adiponectin are recently discovered peptides that are both associated with energy homeostasis and insulin action. In addition, circulating levels of both peptides are altered in obese populations and are associated with poor health. Moreover, expression of ghrelin and adiponectin returns to normal levels following weight loss in obese patients. Because exercise training improves the health status of obese individuals and is associated with reduction of body weight, there is interest in the effects of exercise on adiponectin and ghrelin and whether these peptides may provide better understanding of how exercise improves health. Ghrelin levels do not increase in response to acute running and cycling in humans, and therefore ghrelin does not appear to regulate growth hormone (GH) release during exercise. There is some evidence that ghrelin levels are suppressed following resistance exercise of moderate intensity and are lower with higher GH concentrations during aerobic exercise. It has been suggested that negative feedback from elevated GH produces the reductions, but why these responses have not been consistently found in other studies and whether postexercise reduction in ghrelin affects appetite warrants further investigation. There are a few studies (but not all) that suggest long-term chronic exercise produces increases in ghrelin levels when weight loss is produced. Ghrelin levels are much higher in amenorrheic athletes than in ovulating exercisers or in female exercisers with a luteal phase defect, suggesting an association with reproductive function. Adiponectin concentrations do not change in response to moderate and strenuous running or low- and moderate- intensity cycling. Most studies have revealed that chronic exercise that improves fitness levels, increases insulin sensitivity, and reduces body weight, will increase resting adiponectin levels. However, it does not appear that changes in insulin sensitivity brought about by moderate exercise training are attributable to adiponectin. Exp Biol Med 232:184–194, 2007

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Recent information regarding endocrine function has revealed much concerning the pathophysiological complexities of obesity and metabolic diseases. Ghrelin and adiponectin, two recently discovered peptides expressed by different tissues, have distinctly different actions. Adiponectin affects postprandial fatty acid levels and hepatic glucose output (1). A low plasma adiponectin concentration is associated with insulin resistance (2, 3). Ghrelin facilitates growth hormone (GH) expression and increases appetite, with plasma levels rising and falling before and after meals (4, 5). Thus, effectively both hormones are associated with regulation of energy balance and insulin action. Moreover, circulating levels of both peptides are suppressed in obese populations with compromised insulin sensitivity (6).

Because exercise training improves the health status of obese individuals and is associated with reduction of body weight, there is interest in the effects of exercise on ghrelin and adiponectin and whether these peptides may provide better understanding of how exercise improves health. Exercise is a potent facilitator for the maintenance of healthy levels of body fat and normal insulin sensitivity. Thus, studies have been conducted to determine how exercise affects these peptides. There is a growing body of

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information regarding these two hormones, and with the increasing prevalence of obesity and the diseases associated with it, the function of these peptides becomes increasingly important. In this minireview, we analyze ghrelin and adiponectin separately by first summarizing their functions and then considering prospective research concerning the effects of exercise on each peptide. This review follows our recent minireview on the related topic of leptin and its relationship with exercise (7).

Ghrelin Discovery and Function

In 1999 the endogenous ligand for the GH secretogogue receptor (GHS-R) from the stomach was purified, identified and named ghrelin (6, 8). Desacyl ghrelin, the nonacylated form, is also found in the stomach and blood; much greater concentrations of desacyl ghrelin are found in the blood than the acylated form (6). It is not known whether a specific receptor exists for desacyl ghrelin, although this form and the acylated form will both bind to the h9c2 cardiomyocyte that does not express the GHS-R. Further study is needed to ascertain whether desacyl ghrelin is biologically active and binds to a yet unidentified receptor (6). Ghrelin is produced mainly in the stomach (9) with more ghrelin-producing cells found in the fundus than pylorus. Ghrelin is also found in other portions of the gastrointestinal (GI) tract, including the duodenum, jejunum, ileum, and colon (10–12), decreasing in concentration to the colon. Since the original observation of ghrelin in the GI tract, numerous studies of ghrelin from other tissues have been reported and include the pancreas, hypothalamus, testis, placenta, lung, cardiomyocytes, and chondrocytes (6, 13–16), but the producing cell type has not been firmly established (3). Clearly, the effects of ghrelin involve multiple tissues that suggest a ubiquitous nature and an important physiological role for this peptide.

Ghrelin has a strong effect on appetite (10, 16–19). When ghrelin is injected into the cerebral ventricles of rats, sharp increases in feeding behavior occur, and it appears to antagonize the action of leptin by activating the hypothalamic neuropeptide Y/Y1 receptor pathway (20). The gene expression of ghrelin is increased in the stomach by fasting and is reduced by feeding, and there are daily increases and decreases in concentrations in humans before and after feeding (4, 5). In humans, the major source of ghrelin is from the fundic area of the stomach, but other sites in the splanchnic bed also contribute to peripheral circulation (21). Concentrations of ghrelin in plasma are related to circulating creatinine, suggesting the kidneys are important for ghrelin clearance and/or degradation (22). Studies in humans and rats have demonstrated a short half-life for circulating ghrelin, with the desacyl form having a half-life of less than 1 hour and most frequently less than 30 mins (23, 24); the active ghrelin (3-octanyl ghrelin or acyl ghrelin) half-life is considerably shorter (25).

Intravenous administration of ghrelin results in GH release in both rats and humans, and is three times more potent than growth hormone releasing hormone (GHRH) in the stimulation of GH release (26, 27). Intravenous ghrelin injection results in GH release from the pituitary within 5–15 mins, and GH then requires approximately 1 hr to return to nadir (11). Not only is stimulation of GH release from direct action of ghrelin or GHRH on the pituitary (8), but ghrelin and GHRH seem to synergistically affect GH release (28–30).

As with GH, there is evidence that human ghrelin secretion is sexually dimorphic. Women have approximately three times greater circulating ghrelin concentrations during the late follicular phase of the menstrual cycle than do normal men (31). There also appears to be an interesting maturational effect on postprandial ghrelin responses with feeding-induced inhibition in adults, but not in children (32), suggesting that its role in appetite regulation changes with age. In addition to the orexigenic properties of ghrelin, Zhang *et al*. (33) recently reported that ghrelin has a coderived peptide from preproghrelin, named obestatin, that functions in an opposing manner to that of ghrelin. This 23–amino acid peptide was isolated from the rat stomach and was also found in rat blood. More work is necessary to reveal the role of obestatin in the multifactoral regulation of appetite.

An orexigenic effect of ghrelin is brought about by stimulation of neurons in the arcuate nucleus of the hypothalamus (20), also the affected site of the appetite-suppressing peptide, leptin. Neuropeptide Y (NPY) and agouti-related protein (AgRP) are produced by orexigenic neurons in the hypothalamus, and their expression is suppressed by leptin (34). However, both NPY and AgRP mRNA expression in the hypothalamus increase with intravertebroventricular injection of ghrelin (17, 18, 20) demonstrating ghrelin's orexigenic action. Additionally, ghrelin's effects are absent in NYP and AgRP knockout mice (35), confirming the mode of action. It has been shown that ghrelin stimulates appetite through activation of NPY/AgRP neurons that express ghrelin receptors (36). This opposes inhibitory signals from insulin, leptin, and peptide YY. Thus, ghrelin is a strong GH secretogogue that is produced in the gastrointestinal tract and has strong orexigenic properties through activation of neuropeptide Y and AgRP neurons in the hypothalamus (8, 9–12, 17). It is sexually dimorphic and has an opposing effect on leptin (31, 35, 36).

The daily pattern of ghrelin is regulated by feeding (37, 38). Plasma ghrelin levels increase before each meal and rapidly decline in the postprandial interval, only to rise again before the next meal. During sleep, ghrelin levels remain constant and are not as elevated as the peaks observed before expected mealtimes. Because subjects in most exercise studies were fasted prior to exercise, they would be controlled for any ghrelin variability prior to or during exercise.

Exercise and Ghrelin

There is much interest in the effect of exercise on ghrelin for several reasons. Exercise is known to be a potent stimulus of GH secretion (39–43), and as mentioned above, ghrelin is a potent GH secretogogue; thus, ghrelin could affect GH responses to exercise and recovery or GH could alter ghrelin levels *via* negative feedback. Additionally, exercise has been shown to affect energy balance, another function of ghrelin. The orexigenic stimulus of ghrelin may be affected by exercise and alter energy balance as well. Finally, exercise results in caloric expenditure that could produce a signal to ghrelin-producing cells in the stomach, affecting appetite and GH regulation. Short- and long-term exercise studies have been conducted to study how ghrelin is affected.

Short-Term (≤60 mins) Exercise. Endocrine responses to 45 mins of cycling at a relatively high intensity (individual lactate threshold) were measured in GH-deficient patients on two occasions with and without (discontinued from evening before) intravenous infusion of GH (0.4 IU; Ref. 44). In a normal control group, exercise elicited a sharp increase in GH, whereas infusion of GH in GH-deficient patients resulted in peak GH concentrations after 45 mins, but there was no GH change in these patients without the GH administration. Ghrelin levels did not change significantly in the patients under either condition, nor did ghrelin levels change in the normal controls; however, ghrelin concentrations were lower during the session in GH-deficient patients with GH infusion compared with the session without infusion. The investigators concluded that circulating ghrelin did not affect exercise-induced GH release, but that GH may inhibit ghrelin expression through negative feedback.

Our research group determined responses of ghrelin GH, insulin-like growth factor 1 (IGF-I), and insulin-like growth factor binding protein-3 (IGFBP-3) to a discontinuous 27-min running protocol of 10 mins at 60% of $\dot{V}O_2$max, 10 mins at 75% of $\dot{V}O_2$max, 5 mins at 90% of $\dot{V}O_2$max, and 2 mins at 100% of $\dot{V}O_2$max in trained males (43). The protocol produced a significant increase in GH and IGF-I compared with a resting trial for the same subjects, but ghrelin levels were unchanged, suggesting no effect of ghrelin on GH responses to short-term exercise. There were, however, significant relationships between ghrelin and IGF-I as well as IGFBP-3, but not GH. We concluded that acute (short-term) running at moderate to higher intensities does not stimulate increases in circulating ghrelin and does not play a role in exercise-induced increases in GH, but that more study was required to determine the reason for the relationships between ghrelin and IGF-I as well as IGFBP-3 under these exercise conditions.

Schmidt *et al.* (45) measured GH and ghrelin responses to a low-, moderate-, and high-intensity treadmill test and reported increases in GH, but no change in ghrelin, with each exercise intensity. The investigators concluded that ghrelin is not associated with GH regulation during exercise. Kallio *et al.* (46) investigated GH and ghrelin in response to a 30-min graded cycling protocol that peaked at 80% of $\dot{V}O_2$max in patients with leucine 7 to proline 7 (Leu7/Pro7)-polymorphism and normal controls. The mutation affects the signal peptide of NPY and is associated with high blood lipid concentrations and accelerated rate of atherosclerosis as well as diabetic retinopathy. Although GH increased in both groups, with a 54% greater rise in Leu7/Pro7-genotype patients than in control patients and normal controls, ghrelin levels did not respond to exercise in either group. The authors surmised that ghrelin does not affect the GH response to exercise in healthy males, with the assumption that the regulation sensitivity of the GH system is unchanged.

A recent study reported effects of feeding versus fasting on leptin and ghrelin and cardiorespiratory responses to 15 mins of graded cycling reaching 150 W, which is a low to moderate exercise intensity (47). Changes in GH induced by exercise were not associated with concurrent changes in ghrelin, leptin, or insulin in either fed or fasted state, but a significant pre-exercise relationship existed between insulin and ghrelin in the fed state. Fasting was associated with an attenuated heart rate response to exercise. The authors concluded that leptin and ghrelin have no effect on fasting-associated reduction of heart rate during exercise.

In an animal model study, male rats ran for 30 or 60 mins on a treadmill (22 m/min, 10% slope) or rested (48). Exercise reduced muscle and liver glycogen and plasma ghrelin increased 40% with exercise; however, levels of the gut hormone fragment peptide $YY_{3–36}$ (PYY), which reduces appetite, were unchanged. Hypothalamic total AMP-activated protein kinase (AMPK) activity, which is involved with the regulation of food intake, and phosphorylation state of the AMPK substrate acetyl-CoA carboxylase were not changed after exercise. It was concluded that an hour of exercise elevates ghrelin concentrations in rats, but does not alter hypothalamic AMPK activity.

Resistance Exercise. We recently compared GH, ghrelin, and related glucoregulatory peptide responses to concentric (shortening) and eccentric (lengthening) contractions using the same workload (49). Subjects completed 4 sets of 12 repetitions of 4 different resistance exercises at a 10 repetition maximum workload for either concentric or eccentric muscle actions. Concentric contractions produced greater increases in GH than eccentric contractions; glucose and insulin increased regardless of the form of contraction, but amylin and C-peptide did not change. Ghrelin did not change in response to either trial, but significantly declined during recovery from the concentric trial. The results suggested that perhaps the greater GH response suppressed ghrelin levels during recovery *via* negative feedback. We concluded that (i) ghrelin does not affect GH responses to moderate-intensity resistance exercise, (ii) concentric muscle actions may lead to a suppression of ghrelin, and

(iii) glucose and insulin are not related to postexercise ghrelin suppression.

Takano *et al*. (50) investigated effects of reduced blood flow in muscle during resistance exercise. A specially-designed belt was applied to the proximal end of both legs to reduce blood flow, and 11 young males completed bilateral leg extension exercise at 20% of a 1 repetition maximum. GH and IGF-I increased with exercise but ghrelin concentrations were unchanged. Thus, ghrelin was not associated with activation of the GH–IGF-I axis that was stimulated by low-intensity resistance exercise and reduced blood flow induced through partial vascular occlusion.

In summary, data from the acute exercise studies suggest that ghrelin levels do not increase in response to running and cycling, and therefore ghrelin does not appear to regulate GH release during exercise. There is some preliminary evidence that ghrelin levels are suppressed following resistance exercise of moderate intensity and are lower with higher GH concentrations during aerobic exercise. It has been suggested that negative feedback from elevated GH produces the reductions, but why these responses have not been consistently found in other studies and whether postexercise reduction in ghrelin affects appetite both warrant further investigation. Running-induced increases in ghrelin concentrations in rats have been reported. Whether these shifts are because of inherent differences between rats and humans or differences in research protocols remains to be revealed.

Chronic Exercise. Because weight loss from reduced caloric intake increases circulating ghrelin concentrations (51, 52), several studies have examined changes in ghrelin with chronic exercise (exercise training) and a standardized food intake regimen. A recent study followed 173 postmenopausal, sedentary, overweight women who completed either a 1-year aerobic exercise intervention or a stretching control regimen without reducing caloric intake (53). Exercising women lost significantly more weight (1.4 $\pm$ 0.4 kg) than the control group and showed a steady increase in circulating ghrelin concentrations. In another study of weight loss, Leidy *et al*. (54) determined changes in ghrelin over 3 months in normal-weight women who exercised. Women who lost weight revealed greater ghrelin increases than those who exercised but were weight stable. The authors concluded that ghrelin was very sensitive to changes in body weight, as has been reported for leptin.

Because ghrelin is one of the peptides that functions to regulate energy homeostasis, and because energy balance is known to affect reproductive function as well as the circadian rhythm of the satiety hormone, leptin (55, 56), a study was conducted to ascertain whether ghrelin concentrations in premenopausal women varied in women with different menstrual cycle status (57). In amenorrheic exercising women, ghrelin levels were 85% higher than in women in 3 other groups who were ovulating and sedentary, ovulating and exercising, or exercising with a luteal phase defect. The authors concluded that ghrelin was a potential discriminator between amenorrheic athletes and athletes with other menstrual disturbances. In an earlier study, Laughlin and Yen (58) had reported that the leptin circadian rhythm was surprisingly absent in amenorrheic athletes, but the normal rhythm was present in both normal controls and athletes who continued to have normal cycles. Clearly, these newly described hormones related to adiposity, satiety, and energy expenditure have some relationship to amenorrhea in athletes.

Morpurgo *et al*. (59) investigated whether a 3-week body weight reduction program in severely obese males and females that consisted of exercise, dietary restriction, and psychologic counseling affected ghrelin levels. The 3-week regimen led to reduced body weight, body mass index (BMI), and leptin levels but was not accompanied by a change in ghrelin, either fasting or postprandial. In another study, 12 sets of monozygous twins were overfed by 84,000 kcal over a 100-day period, whereas another 7 pairs of monozygotic twins completed regular exercise training resulting in a 53,000-kcal negative energy balance over a 93-day period (60). The authors reported a nonsignificant reduction in ghrelin in the overfed group, a nonsignificant increase in the exercise/negative-energy-balance group, and no relationship between degree of weight change and ghrelin.

Thus, long-term chronic exercise produces increases in ghrelin levels, especially when weight loss is produced in overweight patients. As of yet, a negative energy balance/weight loss threshold for increasing ghrelin has not been established. Ghrelin levels are much higher in amenorrheic athletes than in ovulating exercisers or in female exercisers with a luteal phase defect, suggesting an association with reproductive function.

Background of Adiponectin

The first description of the cDNA that encoded adiponectin was published in 1995 (61). This was a rapid molecular biology success story, unlike the long biological journey to the discovery of leptin. In the earliest reports from several laboratories, many different names were used (Acrp30, apM1, GBP28, AdipoQ) for what is now generally known as adiponectin; some of these early names may persist in some reports (1).

Adiponectin is a 244–amino acid hormone that is a product of the apM1 gene and is expressed in adipose tissue (62). It is found in high concentrations (5–30 μg/ml) in circulating plasma (62), is associated with levels of saturated and omega-3 fatty acids of dietary origin (63), and is an important factor for central control of energy homeostasis (64). There are two forms in circulation that vary in effect on receptors: a full-length form (fAd) and a proteolytic cleavage fragment of the globular C-terminal domain (gAd) (65, 66). Two adiponectin receptors have been identified, each with different concentrations and affinities (67, 68). The AdipoR1 receptor, with high affinity for the gAd form

of adiponectin and low affinity for the fAd form, is found in high concentrations in skeletal muscle and moderate concentrations in other tissues. The AdipoR2 receptor has intermediate affinity for both forms of adiponectin and is expressed to a greater degree in the liver and much less in other tissues (68).

In contrast to other adipokines, adiponectin expression is reduced in adipose tissue of obese mice and humans (69) and in insulin-resistant patients (70). Circulating adiponectin levels are inversely correlated with percentage body fat and oral glucose tolerance (71); moreover, there is *in vitro* and *in vivo* evidence that adiponectin regulates glucose metabolism and insulin sensitivity through activation of 5′-AMPK (72). In addition to glucose homeostasis, adiponectin is also associated with cardiovascular health, with evidence that reduction in circulating adiponectin levels is correlated with increased prevalence and severity of atherosclerosis (73). These effects of adiponectin on health overlap with those of exercise.

Exercise and Adiponectin

One of the reasons for interest in adiponectin and exercise is the relationship that both adiponectin and exercise have to substrate utilization. Adiponectin reduces the postprandial increase in plasma free fatty acids and affects hepatic glucose output (1). As for exercise, there is interplay between the oxidation of lipids and carbohydrates during exercise, with lower intensities associated with a greater percentage of fatty acid oxidation and higher intensities with greater carbohydrate utilization; exercise intensity also affects the reliance on the form (glycogen or glucose) of carbohydrate oxidized (74). Long-term low- to moderate-intensity exercise stimulates adipocyte hormone-sensitive lipase (HSL) and thus fatty acid mobilization to skeletal muscle for eventual mitochondrial oxidation of fatty acids, through, among other factors, reduction in insulin (*via* gradual and progressive catecholamine stimulation of HSL) and increases in plasma glucagon. The same stimulation of HSL occurs within skeletal muscle. Intramuscular oxidation of glucose during exercise occurs through (i) catabolism of glycogen stores *via* increases in epinephrine affecting the rate-limiting enzyme phosphorylase and (ii) the influence of glucagon on hepatic glycogenolysis and skeletal muscle contraction on glucose uptake (*via* glucose transporter-4) in the muscle as well as accelerated activity of the key glycolytic rate-limiting enzymes.

Adiponectin is associated with increased insulin sensitivity, the major mechanisms of which appear to be increased fatty acid oxidation and inhibition of hepatic glucose production (23). Exercise is known to enhance insulin sensitivity as well. Adiponectin has also been shown to be associated with multiple effects on glucose, lipid, and free fatty acid metabolism in offspring of patients with type 2 diabetes (75). Additionally, greater prevalence and severity of atherosclerosis is associated with low adiponectin levels (73), and regular exercise is known to prevent atherosclerosis and type 2 diabetes.

Thus, recent short-term studies have been conducted to determine the effects of exercise on adiponectin in an effort to determine whether some of the benefits of exercise are produced through mechanisms of changed activity of adiponectin.

Short-Term (≤60 mins) Exercise. We investigated the effects of adiponectin under two conditions (76). In the first experiment, six healthy male subjects completed 30 mins of heavy continuous running exercise at 79% of $\dot{V}O_2$max. In the second experiment, well-trained runners completed strenuous intermittent exercise consisting of treadmill running at 60%, 75%, 90%, and 100% of $\dot{V}O_2$max. A resting control trial for the second experiment was also conducted. Compared with control trials, insulin and glucose did not change in the first experiment, but both increased significantly in the second experiment. Although there was a significant increase in adiponectin in the first experiment, it was no longer significant after correction for plasma volume shifts. In the second experiment, there were significant ($P < 0.05$) changes in adiponectin concentrations over time but not a significant difference between adiponectin responses in exercise and control trials. We concluded that small changes in adiponectin in response to exercise were because of plasma volume shifts and not the exercise regimen *per se*, and that acute (short-term) exercise does not affect circulating adiponectin.

Ferguson *et al*. (77) investigated the acute effects of cycling exercise on adiponectin in healthy men and women. Subjects cycled at 65% of $\dot{V}O_2$max for 60 mins. Adiponectin did not change with the exercise bout in males or females. It was concluded that acute exercise does not affect adiponectin concentrations in women as well as in men. As mentioned earlier, there is interest in adiponectin and exercise because of the effects of both on increases in fatty acid oxidation. In a recent study, 10 subjects completed exercise for 2 hours at 50% of $\dot{V}O_2$max in both a fasting and a nonfasting condition, and plasma samples as well as muscle biopsies were obtained during the protocol (78). The investigators reported no changes in plasma adiponectin levels in response to either trial, nor did expression of muscle adiponectin receptors 1 and 2 differ between trials. However, abundant expression of adiponectin mRNA in muscle and adiponectin was observed with histochemical techniques on the sarcolemmas of skeletal muscle fibers. They concluded that concentrations of plasma adiponectin and the expression in muscle of adiponectin receptor 1 and 2 mRNA are not affected by changes in adipose tissue lipolysis and/or plasma free fatty acid (FFA) concentrations.

Another recent study determined acute adiponectin responses to a 6000-m rowing ergometer test in well-trained athletes (79). Adiponectin, along with leptin and insulin, declined immediately after the exercise bout when corrected for plasma volume shifts (but not for diurnal oscillation), but increased after 30 mins of recovery, while at the same time

there were no changes in plasma leptin or insulin. With regard to diurnal oscillations, the circadian pattern of adiponectin demonstrates a decline during the evening hours and increases by 0800 hours; thereafter, serum levels remain relatively constant until the evening decline (80). It would be expected that, as for leptin, the trivial changes during the timing of these exercise protocols would not be affected, especially if studies were conducted during the morning hours. Long-term protocols, especially if changes in body weight result, might be expected to show an increase in serum adiponectin.

Thus, acute, short-term studies to date demonstrate that adiponectin concentrations do not change in response to moderate and strenuous running or low- and moderate-intensity cycling. Limited data suggest that adiponectin concentrations may decline in response to rowing and that longer bouts of exercise are associated with adiponectin mRNA expression in skeletal muscle. The reasons for these responses remain to be determined.

Chronic Exercise. Elite rowers completed a 6-month training program. Six were selected for a national team and five were not chosen (81). Resting as well as exercise responses to 2000-m sculling were measured before and after training. There were no changes in resting adiponectin levels in selected or nonselected athletes. Adiponectin levels did not change in response to 2000-m sculling in the selected athletes, but was significantly reduced after exercise in the nonselected athletes; leptin followed the same pattern of response. The authors concluded that training may change the adiponectin response to exercise. This is one of the few training studies that have been conducted with normal young men. Other studies have examined the effect of exercise training on adiponectin in older populations or those with diminished insulin sensitivity.

In a study of obese men and women (mean age 63 years), subjects completed treadmill and cycle ergometer exercise 5 days per week, 60 mins per day for 12 weeks (82). Training improved fitness level ($\dot{V}O_2max$), reversed insulin resistance, and reduced leptin concentrations, but did not affect circulating adiponectin levels. These findings are different from those of other training studies that have shown increases in adiponectin with training-induced weight loss and improvement in insulin sensitivity. The reasons for this are unclear.

Overweight and obese adolescents (13.1 $\pm$ 1.8 years) completed a 12-week aerobic training program that improved cardiorespiratory fitness ($\dot{V}O_2max$) by 18% (83). Although body weight and percentage body fat did not change, lower body lean body mass and insulin sensitivity were increased with training. However, serum adiponectin, interleukin (IL)-6, and C-reactive protein (CRP) did not change, and the authors concluded that the improvement in insulin sensitivity was not because of changes in adiponectin.

Severely obese subjects completed a 15-week intervention including a hypocaloric diet and exercise with samples of blood, adipose tissue, and skeletal muscle collected before and after the treatment (84). The intervention reduced body weight and increased insulin sensitivity. Plasma CRP, IL-6, IL-8, and adiponectin increased, but the exercise treatment did not affect adiponectin receptor 1 and 2 mRNA in adipose tissue or skeletal muscle. It was concluded that diet modification and exercise increased adiponectin levels and that low levels of adiponectin in adipose tissue and plasma of the severely obese subjects appear not to be related to increases in macrophage infiltration in adipose tissue, but instead to be related to inhibitory effects of TNF-α and IL-6 released from the macrophages in the adipose tissue.

Kondo *et al.* (85) followed 8 young obese female subjects over a 7-month exercise program that expended 200–400 kcal/day, 4–5 days/week. The subjects' exercise decreased BMI, percentage fat, leptin, and TNF-α and increased adiponectin levels. Thus, this exercise-training program was of a sufficient caloric expenditure and duration to reduce body fat and increase adiponectin concentrations in young obese female subjects.

Yokoyama *et al.* (86) followed a group of middle-aged type 2 diabetic patients who completed either supervised nutritional therapy or nutritional therapy and cycling/walking exercise 5 days per week for 3 weeks. Body weight did not change in either group; in the exercise group, insulin sensitivity was improved, but adiponectin levels did not increase. As such, loss of body weight may be required for increases in adiponectin to occur.

An exercise and a nonexercise, gastric bypass surgery group were compared for insulin levels after training or weight loss (87). Following a 6-month training program for subjects who did not lose fat mass, there were lower circulating insulin levels and greater insulin sensitivity, but no change in resting adiponectin levels. However, insulin and adiponectin levels were significantly related, although plasma adiponectin was not related to BMI or fat mass. In contrast, a nontraining group examined before and after weight loss revealed increases in adiponectin and improved insulin action. The authors concluded that adiponectin does not affect exercise-induced improvements in insulin sensitivity.

Boudou *et al.* (88) trained middle-aged men with type 2 diabetes for 8 weeks with endurance and intermittent exercise. Subjects lost 44% of their abdominal fat and improved insulin sensitivity by 58% with no change in body weight. No changes in leptin or adiponectin were found compared with a control group of diabetics who did not train. Although body fat was reduced, the training lasted only 2 months, a shorter time period than that of other studies that have shown training-induced increases in adiponectin.

In a 2-year randomized (89), single-blind study, 120 premenopausal obese women were assigned to an intervention group that received information related to control of

weight through a reduced-calorie Mediterranean diet and increased physical exercise, and the control group was given more general information about healthy food and exercise. In the intervention group there was a reduction in BMI and subjects revealed lower serum IL-6 and C-reactive protein concentrations, with an increase in adiponectin levels. The authors concluded that the nutritional/exercise program resulted in reduced body weight and reduced markers of vascular inflammation and insulin resistance.

In a study of Finnish servicemen who were on a high-caloric diet for 6 months, only those subjects with the Ala allele of Pro 12 Ala polymorphism of the peroxisome proliferator-activated receptor gamma 2 (PPARgamma2) gene showed significant increases in adiponectin with heavy-exercise–induced weight loss. This study revealed the importance of combined genetics and environment on adiponectin regulation (90).

Fatouros *et al.* (91) examined resistance-training adaptations over the course of a year on adiponectin and leptin in older men (65–78 years) with BMIs of 28.7–30.2. Men were randomly assigned to 4 different training groups: control group and low-, moderate-, and high-intensity training. Energy expenditure during exercise, $\dot{V}O_2$max, and strength improved in all training groups in a training-intensity–dependent manner, whereas skinfold sum and BMI, both expressions of obesity, decreased to a greater degree with high- as compared with moderate-intensity training. Leptin was reduced for all training groups, whereas adiponectin increased only in the high-intensity training group. The authors concluded that resistance training as well as detraining could change adiponectin and leptin in a training-intensity–dependent manner. It is perhaps important to note that the beneficial adiponectin changes with high-intensity training were not lost with short-term detraining, suggesting that a small amount of training may have a positive effect on adiponectin. This study was unique in that it was resistance exercise that was used to produce the training adaptation.

Thus, a number of training studies have been conducted with different populations, including obese men and women, type 2 diabetic patients, gastric bypass patients, and elite rowers. These studies reveal mostly that chronic exercise that improves fitness levels, increases insulin, and reduces body weight will increase resting adiponectin levels if the training program is extended for longer than 2 months and is accompanied by weight/fat loss. It does not appear that changes in insulin sensitivity brought about by moderate exercise training are affected by adiponectin. There is preliminary evidence that resistance exercise training that results in weight loss may increase adiponectin levels as well (91). Given these findings, it is interesting to note that even modest weight loss without exercise seems to increase adiponectin levels. Specifically, Valsamakis *et al.* (92) treated obese subjects for 6 months with sibutramine or orlistat. The sibutramine group lost 5.4% of body weight and the orlistat group lost 2.5%, with both groups having an increase in serum adiponectin. Moreover, in a rodent study, rats (93) were placed on a caloric-restrictive diet without weight-loss drugs for 2, 10, 15, and 20 months that resulted in increases in plasma adiponectin. Taken together, these studies suggest that weight loss produced by exercise, and not exercise *per se*, may be the driving mechanism for increases in adiponectin. There is some evidence that in subjects with A1a allele of Pro 12 A1a polymorphism of the PPARgamma2 gene, exercise-induced weight loss leads to increases in adiponectin. In summary, training studies point to a beneficial effect on adiponectin, which is only seen with greater training volume.

In conclusion, preliminary evidence suggests that both ghrelin and adiponectin are affected by a higher volume of chronic exercise. Short-term aerobic exercise does not appear to affect ghrelin concentrations in response to moderate- and high-intensity exercise, and many studies suggest that ghrelin does not affect GH responses. One study has demonstrated a decline in ghrelin following concentric muscle actions during resistance exercise (49); however, this response does not seem to be related to negative feedback from GH release. Studies are needed to determine whether long-term exercise eliciting a negative caloric balance may affect ghrelin levels and therefore appetite. Moreover, in current studies, the measurement of total ghrelin, with an excess of the des-acylated form, may mask the small changes in the active form that is the component that drives ghrelin action. Because the octanylated form of ghrelin seems to be the active form, and total ghrelin includes only a small percentage (presumably less than 10% of the active form) with a large excess of the des-acylated (unacylated) form of ghrelin (6), studies of the octanylated form are needed to truly understand the physiological impact of ghrelin. Regarding chronic exercise, evidence suggests that exercise training increases ghrelin levels, especially in patients that lose weight. More studies are needed to determine the degree of training required to alter ghrelin expression. The effect of these changes in ghrelin upon appetite and/or whether ghrelin resistance exists in sedentary individuals, similarly to leptin, remains to be determined.

Adiponectin does not increase in response to short-term exercise; however, data that suggest short-term exercise may reduce adiponectin levels are limited, and longer bouts of exercise may be associated with greater adiponectin mRNA in skeletal muscle. Further studies are required that probe deeper into the roles of exercise intensity and duration and determine whether acute changes in adiponectin occur with very large caloric expenditure. There is evidence that adiponectin in a resting condition may affect the balance between the degree of lipolysis and lipogenesis (94). However, a number of studies have not found acute changes in adiponectin during exercise of moderate intensity that would enhance FFA mobilization (*via* insulin suppression–induced increase in HSL activity, etc.). Future studies are required to determine whether training-induced alteration of

adiponectin affects lipolysis during exercise and lipogenesis following exercise. The majority of studies suggest that training greater than 2 months that employs enough exercise volume (frequency, intensity, and duration) to reduce body weight and increase insulin sensitivity will increase adiponectin levels. The studies cited above point to a beneficial effect on adiponectin, which is seen only with adequate exercise volume for longer than a 2-month period. Whether chronic exercise indirectly alters adiponectin expression *via* reduction in body weight rather than a direct effect on upregulation in adipose tissue remains to be determined.

Further studies seem to be required that delve more deeply into the role of long-term chronic exercise on adiponectin and establish whether a weight loss threshold exists. In a series of recent reports, it has been demonstrated that adiponectin circulates as a high–molecular-weight (HMW) and a low–molecular-weight (LMW) form and that recent assay modifications have become available to distinguish these different molecular weight components (95). The basic monomeric unit of adiponectin encoded by DNA is not found in nature, but is a series of posttranslational changes resulting in trimers and larger aggregates of these trimeric units. LMW adiponectin is a hexamer (or dimer-trimer) of 180 kDa, and the HMW form represents 12–18 monomeric units and can be 360 kDa or greater. Recent studies have suggested that the HMW form of adiponectin represents the biologically active form in the circulation and results in a better correlation to clinical situations such as insulin resistance and type 2 diabetes (96). Future studies in the area of exercise physiology must move in this direction as well, and we expect, with the availability of commercial techniques for HMW adiponectin, that these studies will be forthcoming.

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