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Peripheral signals of energy homeostasis as possible markers of training stress in athletes: a review

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Abstract

The importance of physical exercise in regulating energy balance and ultimately body mass is widely recognized. There have been several investigative efforts in describing the regulation of the energy homeostasis. Important in this regulatory system is the existence of several peripheral signals that communicate the status of body energy stores to the hypothalamus including leptin, adiponectin, ghrelin, interleukin-6, interleukin-1β, and tumor necrosis factor–α—different cytokines and other peptides that affect energy homeostasis. In certain circumstances, all these peripheral signals may be used to reveal the condition of the athlete as the result of several months of prolonged exercise training. These hormone and cytokine concentrations characterize a physical stress condition in which different hormone and cytokine responses are apparently linked to changes in physical performance. The possibility to use these peripheral signals as markers of training stress (and possible overreaching/overtraining) in elite athletes should be considered. These measured hormone and cytokine levels could also be used to characterize the physical stress of single exercise session, as the hormone and cytokine response to exercise may actually be a response to the concurrent energy deficit. In summary, different peripheral signals of energy homeostasis may be sensitive to changes in specific training stress and may be useful for predicting the onset of possible overreaching/overtraining in athletes.

1. Introduction

To improve physical performance, athletes often use periods of heavy physical stress followed by a reduction in stress level to achieve specific adaptations at the cellular level. There is a lack of valid determination tools that would reliably aid in monitoring the training process of the athletes and in preventing excessive physical stress that can lead athletes to adverse training outcomes. Evaluation of actual trainability and determination of possible overload and overtraining are among the most complex tasks in sports and exercise sciences. It should be noted that the monitoring process of training is effective only if it has sound scientific foundation.

Assessment of circulating hormones during prolonged physical stress and/or training has received considerable attention due to its implications for general adaptive mechanisms and for physical conditioning [1,2]. Hormonal mechanisms most certainly contribute in mediating both short-term homeostatic control and long-term cellular adaptations to any type of stress imposed on humans [1,2]. Hormones influence the regeneration phase through the modulation of anabolic and catabolic processes after training and exercise [3,4]. To date, regular measurements of hormones of the growth hormone–insulin-like growth factor I (GH–IGF-I) and the hypothalamic-pituitary-gonadal axes have been extensively used to monitor training status and to assess possible development of overreaching and/or overtraining in athletes [5-7]. Different studies have indicated significant relationships of aerobic fitness variables with resting GH secretion [8] and resting IGF-I concentrations [9], whereas resistance training has little or no effect on resting GH or IGF-I concentrations [9,10]. Typically, circulating testosterone and cortisol concentrations in blood are lowered [2,11] or remain relatively constant [7,12] after prolonged endurance training and

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increase after prolonged resistance training [13]. It has been hypothesized that the measurements of these hormone concentrations in blood could assist in determination of adequate dose-response of physical stress after regeneration periods [14,15]. In addition, hormone responses to maximal exercise tests have also been used to monitor heavy training stress in athletes [2,16,17]. However, it has been reported that these hormone responses are not always specific and do not closely mirror the amount of physical stress during the period of heavy training stress and the period of reduced training level in athletes [6,18,19]. These results indicate that the measurement of the anabolic and catabolic hormones to assess the adaptation to existing training load in athletes may be controversial and does not always lead to plausible conclusions.

Acute exercise stimulates the secretion of GH and other components of the GH–IGF-I axis, whereas the secretion of insulin is reduced to allow for the mobilization of carbohydrates and fatty acids needed to meet the increased energy demands during exercise [20]. In particular, exercise stimulates an increase in plasma GH concentration linearly with an increase in exercise intensity [21,22]. However, a large intersubject variability is present in the exercise-induced GH concentration, which is partly related to body composition, energy expenditure, performance level, and type of exercise [23,24]. Exercise also stimulates testosterone and estrogen secretion, which may influence carbohydrate and lipid utilization [25]. In addition, increased testosterone, GH, IGF-I, and thyroid hormone concentrations after exercise contribute to the increased rate of adaptive protein synthesis [26]. Specifically, the muscle cell has to manage the exercise-induced metabolic challenges and cellular adaptations as a result of physical stress [15,26,27]. However, heavy training stress and possible overtraining, which causes a decrease in muscular energy stores and metabolism, may lower protein turnover [15,26,27].

The hypothalamus in the brain appears to centrally integrate the various metabolic, nervous, and hormonal signals and has an important role in the regulation of the central responses to stress and physical training [26]. In response to temporary increases in training stress, some athletes are unable to maintain sufficient intake of calories, thus suffering negative energy balance causing further stress. There have been several efforts to describe the regulation of energy homeostasis [25,26,28]. Regulation of energy balance is an essential function of the human organism that is controlled by the central nervous system and an elaborate interplay of intertissue signaling. Peripheral feedback to the hypothalamus is supplied by different peptide hormones (eg, leptin, adiponectin, and ghrelin) and several cytokines (eg, interleukin-6 [IL-6], interleukin-1β [IL-1β], and tumor necrosis factor–α [TNF-α]). These peripheral signals activate several hypothalamic hormonal pathways [26,28]. Smith [28] proposed that instead of stress hormones, such peripheral signals could be used for the monitoring of athletes to prevent possible overtraining.

This review focuses on the available scientific information on the effects of acute exercise and chronic training on the secretion of peripheral signals of energy balance and inflammation with a focus on the messages generated via peripheral tissues to the hypothalamus, and the possibility of using them as markers of training stress in athletes.

2. Peripheral markers of energy balance

In certain circumstances, signals of peripheral tissues may be used to reveal the condition of the athlete as the result of several months of prolonged exercise training. They represent a physical stress condition whereby different hormonal responses are apparently linked to changes in physical performance. The possibility to use these as markers to monitor training stress (and possible overreaching/overtraining) in athletes should be considered. These markers could also be used to assess the effect of a single exercise session, as the marker response to exercise may actually be a response to the concurrent energy deficit and/or inflammation. Taken together, the marker response to exercise stress may be indicative of excessive training stress (and possible overreaching/overtraining) when it signals (1) negative energy balance and/or (2) inflammation in athletes.

2.1. Leptin responses to acute exercise and chronic training

Leptin is the most studied hormone when describing the energy homeostasis and excessive training stress in athletes [17,29-32]. Leptin, the product of the LEP gene, is primarily secreted by the adipose tissue, acts directly on the hypothalamus, and represents several physiologic functions including regulation of body weight and energy balance [33,34]. There is a positive relationship between adiposity and leptin concentration in sedentary people, but not always in athletes [35,36]. Perhaps the most important function of leptin is its influence on energy balance. In general, leptin decreases when energy intake is restricted, causing energy conservation and decreased thermogenesis [37,38]. In contrast, leptin increases when body fat is increased in an attempt to reduce food intake and exercise thermogenesis [37,38]. Basal leptin is correlated with mean daily energy intake and energy expenditure, demonstrating that leptin can be considered an interface between energy intake and energy expenditure in athletes [39]. Leptin profoundly affects hypothalamic neuroendocrine function as a result of negative energy balance [40]. Specifically, leptin action appears to be regulated through its effect on hypothalamic neuropeptide-Y (NPY) and associated changes in energy balance [33,37,41]. With regard to starvation, NPY expression is increased when leptin levels are low [26,41]. Increased NPY expression depresses the hypothalamic-pituitary-adrenal axis [26]. Accordingly, Steinacker et al [26] suggested that leptin may act as a metabolic hormone and may also have effects on hypothalamic regulation during training in athletes.

A vast body of literature has suggested that body fat reduction is necessary to reduce circulating leptin concentration as a result of exercise training [34,42,43]. Leptin concentrations in athletes appear to be relatively low compared with sedentary individuals [30,31,35,36]. An independent effect of exercise training and increased energy expenditure without changes in body fat content on leptin has also been demonstrated [6,19,44,45]. A negative correlation between leptin and performance [46] and a dose-response relationship of leptin with weekly training volume [17] have been found in rowers. Jürimäe and Jürimäe [46] concluded that relative oxygen consumption during 2000-m rowing ergometer race, which is also a function of body composition, was the main determinant of leptin variance from performance parameters in rowers. These data further demonstrate that leptin is considered to be one of the peripheral signals of energy homeostasis designed to prolong survival in situations such as starvation or heavy physical stress [26]. However, the potential role of leptin in energy homeostasis in response to a prolonged training in endurance-trained athletes has demonstrated contradictory results (Table 1). It is possible that the increase in training volume alone may not be sufficient for the decrease in leptin, as reported by Desgorces et al [51] who found no changes in fasting leptin after an 8-month training season in rowers. The amount of training volume in the study of Desgorces et al [51] in contrast to studies that have observed decreases in leptin [17,19,44,48] was relatively small. The independent effect of negative energy balance on leptin concentration was also demonstrated by Hilton and Loucks [55] who found that the pulsatility of leptin depends on energy availability and that exercise has no suppressive effect on the diurnal rhythm of leptin beyond the impact of its energy cost on energy availability. The absence of an effect of an increase in training volume on leptin has also been described in swimmers over a training season [32]. However, they used rather intensive interval trainings [32] in contrast to low-intensity, high-volume training used in the studies where a decrease in leptin was found [17,19,44,48]. This difference may also partly be due to the different energy systems that are stressed. In intensive interval training, a large amount of energy is derived from carbohydrates, whereas lipids are the main energy source during low-intensity, high-volume training; and the expression of leptin is regulated by the energy flux and triglyceride loss in the adipocyte [56,57].

Rämson et al [48] found that a 2-hour rowing test at the intensity of 80% of the anaerobic threshold (AT) on single sculls caused a decreased postexercise leptin after a 2-week period of increased training volume (ie, 16.5 h wk^{-1}), but not before heavy training (ie, 10 h wk^{-1}) and after recovery periods (ie, 10 h wk^{-1}) in rowers. The diary analysis revealed a negative energy balance of approximately 455 kcal d^{-1} at high-volume period, although they were allowed to eat as much as they liked to individualize their subjective energy demands. However, the results of high–training volume studies support the notion that, during excessive training stress and decreased energy availability, the athlete can be monitored via exercise-induced leptin levels. The performance level of the athlete may also influence postexercise leptin because athletes at higher performance level could go further beyond the limits, thus inducing greater negative energy balance and a greater decrease in leptin [48].

Exercise-induced biochemical changes may be more sensitive to training load than fasting values [1,2,58]. In general, postexercise decreases in leptin can be observed if energy expenditure is high. It has been speculated that the threshold for exercise-induced energy expenditure that is required to disrupt homeostatic fuel regulation resulting in lower leptin is in the proximity of about 400 to 800 kcal, depending on the mode of exercise [59-63]. Decreased leptin concentrations have also been observed immediately after prolonged exercise with an estimated energy expenditure of at least 2800 kcal (eg, marathon run) [64-66]. Leptin concentrations are delayed (about 9 hours) in prolonged exercise or decrease after acute exercise (estimated energy expenditure of at least 850 kcal) in trained subjects [63]. These results suggest that the total work output should be above the threshold reduction in energy availability that must be reached to alter leptin after exercise in athletes.

There are also data showing that postexercise leptin depends on the total body energy availability in athletes. A decrease in leptin was observed after 2000-m maximal rowing (energy expenditure about 120-150 kcal) after 3-week heavy training stress, whereas no decrease was observed during pretraining and after 2-week recovery periods, when the athletes were expected to be well rested [17]. It was believed that at the end of the 3-week heavy training period, the athletes were in an early overtraining state, as the decreased metabolic rate during the 2-week tapering was accompanied by no changes in leptin after the 2000-m rowing test [17]. Similarly, postexercise effect on leptin was observed by Rämson et al [48] after 2-hour rowing at the intensity of about 80% of AT. These results would suggest that heavy training periods had led rowers to the disrupted metabolic homeostasis [1,58], such that the energy expenditure during these single rowing tests was already enough to produce a reduction in leptin. The results also indicate that if hypothalamic down-regulation exists during overreaching/overtraining, analysis of exercise-induced leptin concentrations may provide valuable information for detecting signs of inadequate recovery and excessive training stress.

In summary, it appears that leptin is lowered when energy expenditure during the exercise is about 400 to 800 kcal, depending on the mode of exercise. However, in athletes, leptin could also be lowered after maximal exercise with an estimated energy expenditure of 150 kcal in conditions of limited energy availability. This could be indicative of inadequate recovery resulting in possible overreaching in these athletes. Basal leptin is lowered in endurance athletes

Table 1
Summary of studies linking different markers of energy homeostasis and training status in athletes

Study	Athletes	Time	Study design	Energy status	Markers	Conclusions
Leptin (ng mL^{-1})						
Ishigaki et al [47]	13 Elite distance runners	8 d	HV, training load of 35.5 km d^{-1}	EI 4372 kcal d^{-1}, EE not specified	Resting L ↔ (1.34 vs 1.49 ng mL^{-1})	No change in L due to very low body fat % and probably also due to postprandial measurement time.
Rämson et al [48]	8 Competitive rowers	4 wk	1 Ref wk (~10 h wk^{-1}), 2 wk HV (~18 h wk^{-1}), 1 wk taper (~10 h wk^{-1})	EI 4880 kcal d^{-1}, EE 5329 kcal d^{-1} during 2-wk HV, energy balance: −455 kcal d^{-1}	Fasting L ↓ (from 1.3 to 0.9 ng mL^{-1}), long-distance (2 h) postexercise L ↓ (from 1.1 to 0.8 ng mL^{-1}) after 2 wk HV training. Postexercise L ↔ in ref and taper wk.	At the conditions of excessive training stress and decreased energy availability, fasting and exercise-induced L reflects the condition of the athlete.
Jürimäe et al [17]	12 Competitive rowers	6 wk	1 Ref wk (~9.3 h wk^{-1}), 3 wk HV (~17.5 h wk^{-1}), 2 wk taper (~8.9 h wk^{-1})	Not specified	Fasting L ↓ (from 2.5 to 1.5 ng mL^{-1}), maximal 2000-m postexercise L ↓ (from 1.7 to 1.3 ng mL^{-1}) after 3 wk HV training. Postexercise L ↔ in ref and taper wk.	A dose-response relationship between training volume and fasting L. Postexercise L ↓ indicates inadequate recovery and possible overreaching.
Simsch et al [19]	6 Competitive rowers	9 wk	1 Ref wk, 3 wk HV RT (~16.6 h wk^{-1}), 1 wk taper, 3 wk HV ET (14.3 h wk^{-1}), 1 wk taper	EI 5563 kcal d^{-1} during RT and 5190 kcal d^{-1} during ET	Fasting L ↓ after HV RT (from 1.33 to 1.05 ng mL^{-1})	L ↓ is associated with training volume. Possibility to direct training via monitoring L status.
Noland et al [32]	9 Competitive swimmers	9 wk	Training volume at wk 1, 27 km wk^{-1}; wk 4, 39 km wk^{-1}; and wk 9, 40 km wk^{-1}; mainly high-intensity interval training	EI ~3000 kcal d^{-1} and EE ~4000 kcal d^{-1} at wk 9	Fasting L ↔ during the study period (wk 1, 4.4 ng mL^{-1}; wk 4, 4.3 ng mL^{-1}; wk 9, 4.6 ng mL^{-1})	L is not sensitive to increases in training volume when mainly high-intensity interval training is performed.
Mäestu et al [49]	7 Competitive bodybuilders	11 wk	Weight reduction in preparation for competitions, body fat % ↓ from 9.6% to 6.5% over training period	Maximal energy restriction −980 kcal d^{-1}	Fasting L ↓ from 1.1 to 0.7 ng mL^{-1} for the training period	L is sensitive to initial decrease in body fat but reaches a plateau beyond which there is no further decrease despite increasing negative energy balance.
Jürimäe et al [44]	12 Elite rowers	24 wk	Training load ↑ from 9.9 to 16.8 h wk^{-1} over training period	Not specified	Fasting L ↓ from 1.25 to 0.97 ng mL^{-1} for the training period.	L is sensitive to an increase in training volume even with initially low values
Jürimäe et al [50]	11 Elite rowers	24 wk	Training load ↑ from 12.8 to 16.7 h wk^{-1}. Athletes were divided as SEL (n = 6) and N-SEL (n = 5) for national team.	Not specified	Resting L ↔ in both groups. Maximal 2000-m postexercise L ↔ in SEL and ↓ in N-SEL (from 1.1 to 0.8 ng mL^{-1}) after training period.	Postexercise L ↓ in N-SEL athletes indicates inadequate recovery and perhaps lower performance level.
Desgorces et al [51]	11 Competitive rowers	35 wk	Training load ↑ by 125% in late session.	Negative energy balance −10.5% in late session.	Resting L ↔ over training season.	Training load ↑ does not change resting L. Initial training load may have been too low.
Adiponectin (μg mL^{-1})						
Mäestu et al [49]	7 Competitive bodybuilders	11 wk	Weight reduction in preparation for competition, body fat % ↓ from 9.6% to 6.5%	Maximal energy restriction −980 kcal d^{-1}	Fasting A ↔ during the study period (wk 1, 8.0 μg mL^{-1}; wk 6, 7.1 μg mL^{-1}; wk 11, 8.2 μg mL^{-1}).	Fasting A is not sensitive to the decrease in body fat in athletes with already low initial body fat % values.
Jürimäe et al [44]	12 Elite rowers	24 wk	Training load ↑ from 9.9 to 16.8 h wk^{-1} for the training period	Not specified	Fasting A ↔ for the study period (23.1 vs 27.0 μg mL^{-1}).	Fasting A is not sensitive to heavy changes in training volume. However, the higher initial A levels may have influenced the results.

Jürimäe et al [50]	11 Elite rowers	24 wk	Training load ↑ from 12.8 to 16.7 h wk^{-1}. Athletes were divided in SEL (n = 6) and N-SEL (n = 5) for national team.	Not specified	Resting A↔ in both groups. Maximal 2000-m postexercise A ↔ in SEL and ↓ in N-SEL (from 24.0 to 19.0 μg mL^{-1}) after training period.	Postexercise A ↓ in N-SEL athletes indicating inadequate recovery and also poor performance level.
Ghrelin (pg mL^{-1})						
Rämson et al [48]	8 Competitive rowers	4 wk	1 Ref wk (~10 h wk^{-1}), 2 wk HV (~18 h wk^{-1}), 1 wk taper (~10 h wk^{-1})	EI 4880 kcal d^{-1}, EE 5329 kcal d^{-1} during 2 wk HV, energy balance −455 kcal d^{-1}	Fasting G ↔, long-distance (2 h) postexercise G ↔ (819 vs 823 pg mL^{-1}) after 2-wk HV training. Postexercise G ↑ (from 756 to 884 pg mL^{-1}) in taper wk.	In excessive training stress and decreased energy availability, increases in fasting and exercise-induced G are down-regulated. Probably not suitable for monitoring training.
Mäestu et al [49]	7 Competitive bodybuilders	11 wk	Weight reduction in preparation for competitions, body fat % ↓ from 9.6% to 6.5% for the training period	Maximal energy restriction −980 kcal d^{-1}	Fasting G ↑ from 1148 to 1521 pg mL^{-1} for the training period.	G is sensitive to initial decrease in body fat % but reaches a plateau beyond which there is no further increase despite negative energy balance.
IL-6 (ng mL^{-1})						
Robson-Ansley et al [52]	8 Competitive triathletes	4 wk	wk 1: NT (~18 h wk^{-1}); wk 2: intensified training (NT + 3 × 1 IT); wk 3: NT + 3 × 2 IT); wk 4: NT.	Not specified	Resting IL-6 ↑ (from ~1.0 to ~5.0 ng mL^{-1}) during 2 wk of intensified training period	Acute period of intensified training, which incorporates interval training, induces ↑ in IL-6. IL-6 ↑ indicator of excessive training stress as result of increased training intensity.
Rämson et al [48]	8 Competitive rowers	4 wk	1 Ref wk (~10 h wk^{-1}), 2 wk HV (~18 h wk^{-1}), 1 wk taper (~10 h wk^{-1})	EI 4880 kcal d^{-1}, EE 5329 kcal d^{-1} during 2-wk HV, energy balance −455 kcal d^{-1}	Fasting IL-6 ↔, long-distance (2 h) postexercise IL-6 ↑ similarly at all measurement times.	Not sensitive marker for monitoring training in conditions of increased low-intensity training volume.
Halson et al [53]	8 Competitive cyclists	6 wk	wk 1 and 2: NT (~7 h wk^{-1}); wk 3 and 4: intensified training (~14 h wk^{-1}); and wk 5 and 6: taper (~3.5 h wk^{-1}).	Not specified	Fasting IL-6 ↔ (0.5 vs 0.8 ng mL^{-1}) for the study period.	Not sensitive marker for monitoring training in conditions of increased training volume.
Main et al [54]	8 Elite rowers	8 wk	wk 1-wk 6: HV (24.8 wk^{-1}, 3.5 h d^{-1}) and wk 7 (2.4 h d^{-1}) and wk 8 (1.8 h d^{-1}): taper	Not specified	Posttraining IL-6 ↔ (2.3 vs 3.3 ng mL^{-1}) for the study period.	Not sensitive marker for monitoring training in conditions of increased training volume.
TNF-α (pg mL^{-1})						
Rämson et al [48]	8 Competitive rowers	4 wk	1 Ref wk (~10 h wk^{-1}), 2 wk HV (~18 h wk^{-1}), 1 wk taper (~10 h wk^{-1})	EI 4880 kcal d^{-1}, EE 5329 kcal d^{-1} during 2-wk HV, energy balance −455 kcal d^{-1}	Fasting TNF-α ↔, long-distance (2 h) postexercise TNF-α ↑ (from 1.3 to 2.1 pg mL^{-1}) after 2-wk HV training. Postexercise TNF-α ↔ in ref and taper wk.	Fasting TNF-α is not sensitive marker of monitoring training in conditions of increased training volume. However, postexercise TNF-α ↑ may indicate excessive training stress.
Halson et al [53]	8 Competitive cyclists	6 wk	wk 1 and 2: NT (~7 h wk^{-1}); wk 3 and 4: intensified training (~14 h wk^{-1}); and wk 5 and 6: taper (~3.5 h wk^{-1}).	Not specified	Fasting TNF-α ↔ (6.3 vs 8.3 pg mL^{-1}) for the study period.	Fasting TNF-α is not sensitive marker for monitoring training in conditions of increased training volume.
Main et al [54]	8 Elite rowers	8 wk	wk 1-wk 6: HV (24.8 h wk^{-1}, 3.5 h d^{-1}) and wk 7 (2.4 h d^{-1}) and wk 8 (1.8 h d^{-1}): taper	Not specified	Posttraining TNF-α ↑ peaked at wk 6 (1.3 vs 2.4 pg mL^{-1}).	Posttraining TNF-α ↑ may indicate increased training stress.

A=adiponectin; EE=energy expenditure; EI=energy intake; ET=endurance training; IL-6=interleukin-6; IT=interval training; G=ghrelin; HV=high volume; L=leptin; N-SEL=not selected for national team; ref=reference; NT=normal training; RT=resistance training; SEL=selected for national team; TNF-α = tumor necrosis factor-α : wk=week; ↑ indicates significant increase; ↓ indicates significant decrease; ↔ indicates no change.

and related to mean daily energy intake and energy expenditure, indicating that leptin could be considered an interface between energy intake and energy expenditure in these athletes.

2.2. Adiponectin responses to acute exercise and chronic training

Adiponectin is probably the most abundant adipose tissue–specific factor and has been implicated in the regulation of energy homeostasis in combination with leptin [67]. In contrast to other adipocytokines, adiponectin expression is negatively regulated in obesity [33,68,69]. Its circulation is inversely correlated with body fat [70] and, more specifically, with central adipose tissue stores [71]. Adiponectin exists in 3 major oligomer forms: a low–molecular-weight, a medium–molecular-weight, and a high–molecular-weight form [72,73]. It has been suggested that the high–molecular-weight adiponectin is more active [74] and better correlated with variables related to glucose and lipid metabolism than total adiponectin concentration [75]. Based on results with athletes, it could be postulated that different adiponectin oligomers may also change, similarly to total adiponectin [72,76]. Unfortunately, not many studies have investigated the pattern and forms of adiponectin during training in athletes (Table 1).

In general, adiponectin concentrations increase during periods of weight reduction in obese subjects [77]. In contrast, Mäestu et al [49] demonstrated that adiponectin was not changed during a weight reduction period of 10 weeks in bodybuilders during conditions of limited energy availability in which a mean 4.1-kg loss of body fat was observed in preparation for national championships. One possible explanation may be that adiponectin is mainly secreted by visceral fat that is considered metabolically more active than subcutaneous fat [78]. Therefore, the weight management generating low body fat values in athletes may have less impact on visceral fat than on subcutaneous fat. These results suggest that basal adiponectin is not a good marker of energy homeostasis in lean and very lean athletes, where the competition result also depends on a specific weight category.

To our knowledge, the only studies that have investigated the role of adiponectin as the possible marker of energy homeostasis in response to prolonged training periods in athletes have been performed with rowers [44,50]. Training in rowing during the preparatory phase is characterized by low-intensity, high-volume sessions to improve aerobic capacity [3,5]. Thus, it is well suited to investigate a possible adiponectin and exercise interaction during prolonged training periods at relatively high daily energy expenditures. A 6-month volume-extended training period showed only a trend for an increase in adiponectin despite an increase in training stress [44]. This could be explained by the fact that well-trained athletes present relatively high baseline adiponectin concentrations [44,50] compared with the baseline adiponectin levels in healthy but less-trained subjects [76,79]. In addition, as blood adiponectin concentrations depend on adiponectin synthesis in adipose tissue and its clearance in plasma, the lack of alterations could not rule out the possibility that the expression of the adiponectin gene in adipose tissue is not affected in response to heavy training stress [50]. Studies with obese people have demonstrated significant increases [80,81] or no change [82,83] in circulating adiponectin concentration as a result of prolonged exercise training.

Increased training stress over a preparatory phase in rowers may modify adiponectin response to a bout of a 2000-m maximal sculling without having an effect on the resting adiponectin [50]. According to the results of a study by Jürimäe and colleagues [50], short-duration maximal exercise-induced adiponectin concentration may be indicative of the amount of physical stress and consequently may affect the condition of the athletes. Lowered adiponectin as a result of 2000-m maximal sculling at the end of the 6-month preparatory phase in lower-performance rowers may be a sign of inadequate recovery and inadequate performance level of these athletes. In contrast, higher-performance rowers demonstrated higher exercise-induced adiponectin concentrations compared with the corresponding adiponectin values obtained before the 6-month preparatory period [50]. These findings suggest that higher-performance athletes were able to adequately recover from previous trainings. This also suggests that training could modify adiponectin response depending on the performance level of athletes and that decreases in postexercise adiponectin may be a sign of inadequate recovery. However, further studies are needed before any conclusions may be made.

To our knowledge, only 4 studies have investigated the effects of different modes (ie, running and rowing) and duration of acute exercise on adiponectin in well-rested athletes [50,84-86]. In the Kraemer et al [86] experiment, well-trained runners completed strenuous running at 60%, 75%, 90%, and 100% of maximal oxygen consumption ($V_{O_{2max}}$), which elicited a small (10%) but significant increase in postexercise adiponectin. However, after correcting for hemoconcentration, the increase was no longer significant. Kraemer et al [86] concluded that changes in adiponectin in response to exercise occurred because of plasma volume shifts and not as the result of the exercise regimen per se, and that acute short-term exercise does not affect adiponectin levels in well-trained runners. In contrast, we have demonstrated that adiponectin could be regarded as a signal for metabolic reaction to on-water sculling at the level of individual AT and the following recovery in rowers [85]. Specifically, a mean of approximately 15% increase in adiponectin concentration occurred after the first 30 minutes of recovery of on-water sculling at 75% $V_{O_{2max}}$ for approximately 30 minutes [85]. Similarly, another study also demonstrated a delayed increase in adiponectin after the first 30-minute recovery of maximal 6000-m ergometer rowing (~20 minutes) [84], whereas no postexercise changes

were observed after maximal 2000-m single sculling (~7 minutes) [50] in well-rested elite male rowers. The results of these acute exercise studies with athletes and also with healthy controls [79] suggest a delayed exercise response in adiponectin during postexercise recovery where larger caloric expenditure is needed.

In summary, it appears that adiponectin presents a delayed exercise response during recovery after acute exercise with larger energy expenditure in athletes. Well-trained athletes also have relatively high baseline adiponectin concentrations. Therefore, basal adiponectin seems to remain stable in the conditions of high training stress and limited energy availability. Accordingly, basal adiponectin is not a good marker of energy homeostasis in athletes.

2.3. Ghrelin responses to acute exercise and chronic training

Ghrelin is secreted by endocrine cells in the gastrointestinal tract, transfers information from the stomach to the hypothalamus, and influences GH release in response to changes in energy homeostasis [87]. Ghrelin has been found to regulate feeding behavior by modulating expression levels of orexigenic peptides in the hypothalamus [87] and to coordinate energy balance by enhancing appetite and food intake [88,89]. Meal responses of ghrelin are correlated with acute caloric intake over a typical day of eating in normal-weight subjects [90,91]. Ghrelin correlates negatively with body fat mass [92,93] and is responsive to diet- and exercise-induced changes in body mass [91,94,95]. In addition to total ghrelin, acylated and deacylated forms of ghrelin have been found [68]. However, there are no data showing that increases in total ghrelin do not increase acylated ghrelin in humans. It has also been found that total ghrelin and acylated ghrelin are positively correlated [96] and that both forms of the hormone potentially play a role in energy balance [97]. Based on these results, it could be suggested that different forms of ghrelin change similarly to changes in energy balance. However, future studies are needed to better clarify the responses of total ghrelin and its acylated and deacylated forms in various conditions.

There are a number of studies including athletes that have examined the influence of an acute bout of exercise on total ghrelin concentration [21,22,24,39,61,98-103]. Most studies with healthy untrained subjects [22,24,98,102] and also well-trained athletes [21,61,100,103] would suggest that negative energy balance as a result of short-term exercise may not be sufficient to alter ghrelin response. Kraemer et al [21] completed a progressively intense intermittent exercise trial with well-trained runners on a treadmill at 4 exercise intensities: 10 minutes at 60%, 10 minutes at 75%, 5 minutes at 90%, and 2 minutes at 100% of $V_{O_{2max}}$. This study demonstrated no changes in ghrelin concentrations. In a study by Schmidt et al [22], plasma ghrelin concentrations remained unchanged at different workloads (50%, 70%, and 90% of $V_{O_{2max}}$) in young healthy male subjects. In middle-aged healthy men, acute exercise for 45 minutes at the AT level also did not alter circulating plasma ghrelin concentration [24], whereas Burns et al [98] found that plasma ghrelin concentration was not responsive to acute exercise (1-hour bout of high-intensity treadmill running) –induced alterations in metabolism in healthy young adults.

A recent study in our laboratory demonstrated that high-intensity intermittent rowing with an estimated energy expenditure of approximately 400 kcal in 20 minutes increased immediate postexercise ghrelin in elite male rowers, whereas at 30 minutes postexercise, ghrelin concentrations were already decreased to the preexercise level [61]. Assuming that the energy balance drives the specific hormone response, it is conceivable that the measured ghrelin concentrations are related to the exercise-induced energy expenditure. Indeed, the postexercise ghrelin was related to the distance covered ($r = 0.75$, $P < .05$) during a 2-hour endurance rowing training session [39]. These results suggest that exercise bouts used in previous studies [21,22,24,98,100] generated a limited amount of negative energy balance or that using exercise protocols that require relatively high percentage of engaging total muscle mass resulted in a greater energy cost. This may imply that the ghrelin response depends on the amount of total work performed. However, to what extent exercise intensity influences ghrelin response remains to be determined. In addition, Christ et al [99] found that a 3-hour aerobic exercise session on a cycle ergometer at 50% of maximal aerobic power caused a negative energy balance that resulted in a significant increase in total ghrelin concentration in endurance-trained athletes after a low-fat diet (0.5 $g \cdot kg^{-1}$ lipids per body mass) but not a high-fat diet (3.5 $g \cdot kg^{-1}$ lipids per body mass). These results support the hypothesis that if the body energy reserves are limited, a single exercise session with higher energy expenditure may alter ghrelin response in athletes using less overall muscle mass during an exercise session. Taken together, in athletes, a certain threshold reduction in energy availability must be reached before any significant changes in ghrelin concentration could occur; and the amplitude of the ghrelin response could be linked to the energetic status induced by acute exercise.

Kraemer et al [21] suggest that glucoregulatory stress from the acute exercise could result in a suppression of ghrelin concentration during the recovery period. Indeed, some studies that have used more intensive exercise tests have demonstrated reduced values for circulating ghrelin during the postexercise recovery period [101,104-106]. It has been suggested that maximal exercise-induced large increases in insulin [21,101] and GH [101,106] levels may suppress ghrelin concentration during the recovery period. It has also been argued that postexercise ghrelin responses may be independent of changes in energy balance [107] and that acute exercise increases energy intake only after some time postexercise [108]. Another explanation could

be that acute exercise can cause a transient (1-2 hours) suppression of appetite after exercise and that ghrelin may be related to this appetite suppression [108]. Clearly, this issue needs to be investigated further before arriving at any plausible conclusions.

It has also been suggested that ghrelin levels increase in response to exercise-induced or prolonged training-induced weight loss and not because of food restriction per se, acting via a negative feedback loop that regulates body mass [91,94,109,110]. Unfortunately, data on the influence on exercise training are mainly available on obese subjects [109,111,112], whereas only limited data are provided for athletes [21,48,49]. Leidy et al [94] demonstrated that a 3-month 5-days-a-week exercise training program in normal-weight healthy women had no impact on circulating ghrelin even though the participants expended a mean of 486 kcal per exercise bout. It was suggested that exercise training itself had little impact on ghrelin concentration in these weight-stable women [94]. However, it could be hypothesized that if a caloric restriction is apparent during periods of heavy training, ghrelin should also increase in athletes to stimulate appetite and therefore provoke higher caloric intake in conditions of high training load.

In general, only a few studies have investigated ghrelin response to prolonged training in athletes (Table 1); however, a few preliminary suggestions could be drawn. Increases in training volume over 2 weeks were not sufficient to increase fasting ghrelin despite an observed negative energy balance of approximately 500 kcal d^{-1} in rowers [48]. This may indicate that fasting ghrelin is not sensitive to temporarily increased training volume. However, our recent study with bodybuilders demonstrated that ghrelin increases in well-trained athletes with relatively low body fat mass but reaches a plateau beyond which there is no further increase in ghrelin despite continuing negative energy balance and body mass loss [49]. It could be postulated that during specific metabolic conditions resulting from the preceding high-volume training with high energy expenditure, negative energy balance, temporarily restricted caloric condition in fasting state, and perhaps low body energy reserves (ie, low body fat content) may all contribute to further exercise-induced effect of energy expenditure that leads to down-regulation of ghrelin receptors [48,49]. However, the mechanism of how the preexercise metabolic condition, that is, negative energy balance, influences the postexercise ghrelin concentration has not been established.

In summary, in athletes, an acute bout of exercise may increase ghrelin response when exercise energy expenditure is at least 400 kcal. In addition, the amplitude of ghrelin response could be linked to the energetic status induced by acute exercise; and ghrelin could be used to characterize acute exercise stress in endurance athletes. However, it appears that basal and postexercise ghrelin response is not sensitive enough to represent changes in training volume and energy availability in athletes.

2.4. Inflammatory cytokine responses to acute exercise and chronic training

Excessive training stress, associated with insufficient rest and recovery, may induce acute local inflammatory responses in working skeletal muscle that may evolve into chronic inflammation and produce systemic inflammation [113,114]. Systemic inflammation has been suggested to be the contributing factor of possible overtraining [28]. Specifically, it has been proposed that the muscle cell has to manage the exercise-induced metabolic challenges and stress-induced damage to initiate metabolic adjustments, transport processes, cellular repair processes, and adaptive protein synthesis [26,27,113,114]. Accordingly, systemic inflammation caused by possible overtraining may involve increases in cytokines such as IL-6, IL-1β, and/or TNF-α as part of the hormonal messages emerging from the muscle cell to the circulation [28,114]. Elevated circulating cytokines subsequently may play a primary role in coordinating systemic inflammation, engaging the central nervous system [26,28]. Tissue injury that results from strenuous exercise has been demonstrated to elicit an acute phase response analogous to inflammation [115-117]. This response process may involve the release of different inflammatory-related cytokines [11,28,114].

In recent years, data concerning the effects of acute exercise and exercise training on different inflammatory cytokines, in particular IL-6, have generated considerable interest [113,118]. It is clear that during muscular activity, IL-6 can be produced within [119] and released from [120] skeletal muscle tissue. It has been proposed that different inflammatory cytokines may be involved in the adaptive process as a result of regular exercise [4,114,121-123]. Interleukin-1β and TNF-α are secreted at the onset of an inflammatory cascade and act locally at the site of injury/infection, whereas the other cytokine believed to be involved in heavy physical exercise, IL-6, is generally synthesized after the initial synthesis of IL-1β and TNF-α [28]. Although IL-6 is inducible in nearly every human cell and tissue type [124], its rise after exercise is generated from the working skeletal muscles [113,120,125]. It has been suggested that muscle cells like myoblasts, satellite cells, and in vivo regenerating muscle fibers may produce IL-6 when activated in response to exercise-induced muscle injury [28,113]. In addition, IL-6 contributes to substrate availability and utilization [126] by facilitating an increase in glucose [127] and lipid [128] metabolism to maintain metabolic homeostasis during exercise [121]. However, these regulatory processes are distinct from the effects of systemic spillover of inflammatory cytokines, which mark the failure of local compensation mechanisms [26]. There is now evidence that all these inflammatory cytokines have receptors in the hypothalamus and thus can act directly on the hypothalamic network [129] and may be responsible for some of the symptoms of central fatigue during overreaching and overtraining in athletes [26].

Interleukin-6, TNF-α, and/or IL-1β increase during a single exercise session as the result of an acute inflammatory response [121,123,125,130,131]. The response of these inflammatory cytokines depends on the intensity and duration of the exercise, the amount of muscle mass involved, as well as the subjects' endurance capacity [15,26,113,132]. The magnitude of the changes differs markedly depending on the inflammatory cytokine investigated, as IL-1β and TNF-α increase 1- to 2-fold [26,114,121], whereas IL-6 has been found to increase up to 128-fold after strenuous exercise [113]. In our recent study with rowers, the exercise intensity protocol used (ie, 2-hour rowing at the intensity of 80% AT) may have been less intensive to the working muscles, such that the additional metabolic strain after the 2-week increased training volume was insufficient to induce a more significant increase in postexercise IL-6 [48]. Similar to the study of Starkie et al [133], a 5-fold increase in IL-6 was observed during these rowing trials [48], which appears to be relatively small because about 20-fold [121] and 45-fold [134] increases in IL-6 were observed after competitive cycling. However, Ostrowski et al [130] found a 100-fold increase in circulating IL-6 concentration after a marathon run. Furthermore, 8000-fold increase of plasma IL-6 after an ultradistance foot race of the 246-km "Spartathlon" has been found [116]. The study by Margeli et al [116] provides evidence that IL-6 could be dramatically increased during prolonged exercise to levels seen only in major trauma and systemic inflammation [135,136].

In another study with experienced rowers, no increases in IL-6 and TNF-α were found after a 2-hour rowing in either placebo or carbohydrate conditions in elite female athletes [115], whereas 2.5 hours of running at 77% $V_{O_{2max}}$ caused a mean of 753% and 421% increase in postexercise IL-6 in placebo and carbohydrate conditions, respectively. [137]. Nehlsen-Cannarella et al [137] also reported that carbohydrate vs placebo ingestion was associated with higher plasma glucose and lower plasma cortisol concentrations, suggesting that carbohydrate ingestion attenuates the inflammatory responses to heavy exertion in athletes. It should be noted that much of the IL-6 increases as a result of exhaustive exercise have been studied within the context of prolonged running exercise [116,117,130,138-142] and could not be directly applicable to other athletic training events [54,113]. Accordingly, 1 hour of cycle ergometry at 70% $V_{O_{2max}}$ [143] and 2 hours of intensive resistance training [144] caused no changes in postexercise IL-6. Henson et al [115] suggested that no changes in inflammatory cytokines occur when exercise intensity is not sufficient to induce significant stress hormone response. In accordance with this, Minetto et al [145] found that an acute bout of high-intensity isokinetic exercise elicited a significant increase in cortisol and IL-6 concentrations in elite power and endurance athletes. However, the cortisol response to exercise was not related to the amount of circulating IL-6 levels in these athletes [145]. In addition, a recovery time before an exercise session may affect postexercise increases in IL-6 concentration [146,147]. Specifically, Ronsen et al [147] demonstrated that a second bout of heavy endurance exercise (75 minutes of cycle ergometry at 75% of $V_{O_{2max}}$) on the same day is associated with a more pronounced increase in IL-6 compared with a single bout of similar exercise. Furthermore, a trend toward attenuation in the augmented cytokine response was observed when the rest period between the 2 bouts of heavy endurance exercise was extended from 3 to 6 hours and an additional meal was served [147]. In another study, using a protocol with 3 bouts of exhaustive rowing, each lasting 6 minutes and separated by 4 hours of rest, Nielsen et al [146] also showed a trend toward augmented peak values of plasma IL-6 after each consecutive bout of rowing exercise. The augmented IL-6 response may be linked to glycogen depletion in the working muscle, thus representing a signal of energy shortage in the muscle and a need for increased substrate mobilization from other tissues [146,147]. Accordingly, the postexercise increase in IL-6 appears to be dependent on the preexercise glycogen content of the muscle [120,127,146-148]. Muscle glycogen content also depends on the proper energy intake and energy balance, which suggests that negative energy balance may have an impact on higher IL-6 after exercise due to higher muscular damage caused by reduced energy reserves [48].

Unfortunately, limited evidence exists in the literature describing the reactions of these inflammatory cytokines to the response of prolonged training; and the results are contradictory (Table 1). Stewart et al [149] demonstrated that a 12-week combined aerobic and resistance training program had no effect on fasting IL-6 or IL-1β in healthy previously physically active and inactive subjects. Likewise, no change in IL-6 was observed after 2 [48] and 6 [54] weeks of high-volume training in rowers. Recent theories have suggested that elevated levels of inflammatory cytokines, in particular IL-6, may play a role in fatigue and illness behavior experienced by athletes with unexplained underperformance syndrome [15,150]. Specifically, it has been suggested that athletes with unexplained underperformance syndrome may not necessarily have IL-6 values above the norm but that they exhibit an increased sensitivity to IL-6 as observed in individuals with chronic fatigue syndrome [150]. A study by Robson-Ansley et al [52] showed an increase in IL-6 concentration in response to 2 weeks of intense interval run-training period with an increase in fatigue and general malaise in highly trained male triathletes. However, IL-6 concentration together with other fatigue symptoms returned to baseline within a week of normalized training stress in these athletes [15]. The inflammatory cytokine theory of overtraining [28] suggests that excessive physical exercise can induce an inflammatory response resulting in a chronic elevation of IL-6 in athletes. It may be suggested that under certain conditions elevated levels of IL-6 may be used as markers of possible heavy training stress in athletes.

A recent study in our laboratory examined the response of increased training volume on IL-6 and TNF-α in competitive rowers [48]. This study failed to detect any changes in

fasting IL-6 and TNF-α after 2 weeks of increased training volume. However, a 2-hour rowing at the intensity of 80% of AT increased postexercise TNF-α only after a period of high training volume. In another study, posttraining TNF-α was increased after 6 weeks of high training volume (average training duration of 24.8 h wk^{-1}) in elite rowers preparing for World Championships [54]. Unfortunately, only one blood sample was collected each week posttraining in this study [54], which makes the comparison and interpretation of these results somewhat difficult. The source of TNF-α during exercise has not been definitively revealed, and adipocytes within the muscle may also be an additional source for TNF-α synthesis [151]. Tumor necrosis factor–α is known to stimulate lipolysis in adipocytes and inhibit insulin action on glucose transport [26]. The postexercise increases in TNF-α after high-volume training may indicate higher stress in lipid metabolism due to conditions of higher energy deficit [48]. Accordingly, Halson et al [53] reported that a 2-week period of intensified cycle training followed by a period of recovery did not cause any changes in fasting IL-6 and TNF-α in trained male cyclists. According to these fasting IL-6 and TNF-α results [48,53], it could be postulated that monitoring muscular damage and the resulting inflammation as the initiating event in the development of overtraining [28] may not be useful to detect possible increases in fatigue in these athletes. However, it is possible that higher physical strain for a longer period is needed to cause changes in inflammatory cytokines. Indeed, as additional evidence of inflammatory cytokines in response to exercise is lacking, additional data on athletes are needed to clarify if those markers could be used as signs and markers of prolonged deadaptation that could lead to overreaching and/or overtraining in athletes.

In summary, the most studied inflammatory cytokine appears to be IL-6 in athletes. Interleukin-6, TNF-α, and IL-1β increase during a single exercise session resulting in an acute inflammatory response associated with the intensity and duration of the exercise. Interleukin-6 may have a role in fatigue and illness behavior experienced by athletes with unexplained underperformance syndrome. Postexercise TNF-α may be indicative of increased training stress and inadequate recovery in athletes.

3. Interactions between metabolic hormones

Exercise appears to be a major factor affecting hormonal modulation of energy intake and energy output. Exercise stress increases energy expenditure directly, but also affects a number of hormones and cytokines that control metabolic rate [4,38,107,152]. There is also evidence that various hormones involved in the metabolic control are closely connected in regulatory loops linking the fuel-supplying organs (eg, liver, fat tissue), regulatory centers (eg, β-cell, hypothalamus), and the working muscle cells [26]. The central role of the hypothalamus is clearly identified in integrating a network of hormones regulating metabolic pathways and interacting with the anterior pituitary to determine functional status of many of these hormones [28,38,114]. Furthermore, there is now experimental evidence to suggest that all metabolic hormones have hypothalamic receptors [26,153].

Adiponectin and leptin exert an important role in the hormonal regulation in response to energy expenditure during training in athletes [58]. A feedback regulation has also been suggested between leptin and insulin [154]. Insulin may provide a mechanism by which adipose tissue detects changes in overall energy balance and, in turn, up-regulates or down-regulates leptin gene expression accordingly [155]. Studies in athletes have demonstrated positive associations between leptin and insulin [59,60,100], whereas adiponectin is negatively correlated with leptin [44] and insulin [50]. It has been suggested that insulin is an inhibitor of adiponectin gene expression [156]. When taking into account that insulin has been related to a mean weekly training volume ($r = -0.40$, $P < .05$) in athletes, it can be suggested that the effects of exercise training on insulin could also mediate the adiponectin response to exercise [50]. However, the proposed mechanism linking adiponectin with insulin sensitivity is unclear; and further studies are warranted. It has also been suggested that adiponectin carries signals between adipose and muscle tissues [157]. Adiponectin can activate adenosine monophosphate–activated protein kinase and increase fatty acid oxidation in skeletal muscle [158]. Although total adenosine monophosphate–activated protein kinase activity is related to muscle mass [157], it could be argued that athletes using high muscle mass during acute exercise need more adiponectin to regulate metabolic fluxes [85]. This can be explained by the finding of the 6-month preparatory period of athletes indicating that well-trained athletes present relatively high baseline adiponectin concentrations than nonathletes and that subjects with higher performance levels demonstrate higher exercise-induced adiponectin concentrations [50]. Adiponectin may affect glucose metabolism, and the change in adiponectin as a result of acute exercise may also be due to increased levels of the inflammatory cytokines [85]. However, as there are no complex data yet, the relationship of adiponectin with IL-1β, IL-6, and TNF-α during acute exercise needs further research.

It has been argued that insulin may have a role in ghrelin regulation after exercise in athletes [21]. In contrast, no relationship between insulin and ghrelin concentrations has been observed in rowers [12,39,50]. Similarly, some studies have found that ghrelin is not related to leptin [39,159,160], whereas other studies have found such a relationship [161]. Shintani et al [162] postulated that ghrelin and leptin share the hypothalamic NPY/Y1 receptor pathway. To date, limited evidence exists concerning NPY responses to exercise. Karamouzis et al [40] found an 81% increase and an almost 100% decrease after 25-km marathon swimming in plasma NPY and leptin concentrations, respectively.

Furthermore, a significant negative correlation between the values of leptin and NPY was found; and they concluded that changes in leptin and NPY take place during marathon swimming to compensate for the negative energy balance due to prolonged effort. Significantly higher plasma NPY concentrations were observed in soldiers subjected to the "uncontrollable stress" of interrogation, which produced extreme subjective psychologic distress and clinically significant dissociation [163].

In summarizing current knowledge, we may conclude that acute exercise and chronic training cause some perturbations in different metabolic hormones; however, relatively little is known about the exact interactions between these hormones in athletes. It can be suggested that a number of physiologic and psychologic systems that regulate energy intake and energy expenditure work synergistically to maintain energy balance in the organism. In addition, a number of different circulating peripheral mediators are active in regulating energy homeostasis through different hormonal feedback mechanisms during exercise and training.

4. General conclusions and suggestions for future research

The current information regarding the role of different peripheral signals in energy balance during exercise and training stress seems only to confirm that these peripheral mediators at certain circumstances could be used to monitor both long- and short-term training effects in athletes (Table 2). However, the study of different peripheral mediators of adipose (eg, leptin, adiponectin), muscle (eg, IL-6, TNF-α), and gut (eg, ghrelin) tissues that communicate the status of body energy stores to the hypothalamus has only presently been addressed; and additional work is needed to further clarify the present research findings in this area so that we can fully understand their implications and also use them in athletic training monitoring. In addition, bone tissue has also recently emerged as an endocrine organ with potential effects on body mass, energy expenditure, and glucose homeostasis [164,165]. The central role of the hypothalamus has clearly been identified in integrating a network of metabolic regulating hormones as well as other afferents and error signals [26]. Among others, leptin, adiponectin, ghrelin, IL-6, TNF-α, and also insulin exert important effects on the hormonal regulation in response to acute exercise and chronic training. In addition, it appears that all peripheral mediators mentioned respond to physical exercise and are in some way related to each other. Exercise stress is one of the links between these hormonal modulators of energy balance; and at certain circumstances, these hormonal modulators could be used to describe the condition of the athlete.

To date, much research in this area has been conducted with endurance-trained athletes; and there has been very little research on resistance-trained athletes. Preliminary evidence suggests that basal leptin is reduced in endurance-trained athletes. A dose-response relationship has been found between leptin and weekly training volume, and leptin has also been related to mean daily energy intake and expenditure. In well-rested athletes, a possible decrease in postexercise leptin and increase in postexercise adiponectin and ghrelin depend on the total amount of work performed; and these hormonal modulators could be used to characterize the amount of energy expended during an exercise session. Although postexercise decreases in leptin and increases in ghrelin as the result of a single exercise session may be indicative of excessive training stress, they may also be used as markers of prolonged fatigue and possible overreaching.

A number of discovered peripheral factors that communicate the status of body energy stores to the hypothalamus are markedly higher than reported in this review, and these factors are continuously increasing. For example, visfatin is a newly identified cytokine that could be used to characterize the regulation of energy homeostasis [166], as visfatin has insulin-like metabolic effects that may improve insulin

Table 2
Summary of proposed markers known to change and their suitability for monitoring training status in endurance athletes

Marker	Sampling	Training	Marker	Possible suitability
Leptin (ng mL^{-1})	Fasting	Increased training volume	↓	Indicates heavy training stress
		Increased training intensity	↔	Not sensitive
	Postexercise	Increased training volume	↓	Indicates inadequate recovery and possible overreaching if postexercise changes in leptin are not prevalent in normal training conditions.
Adiponectin (μg mL^{-1})	Fasting	Increased training volume	↔	Not sensitive
	Postexercise	Increased training volume	↓	Indicates inadequate recovery
Ghrelin (pg mL^{-1})	Fasting	Increased training volume	↔	Not sensitive
	Postexercise	Increased training volume	↔	Not sensitive
IL-6 (ng mL^{-1})	Fasting	Increased training volume	↔	Not sensitive
		Increased training intensity	↑	Indicates heavy training stress
	Postexercise	Increased training volume	↑	Not sensitive
TNF-α (pg mL^{-1})	Fasting	Increased training volume	↔	Not sensitive
	Postexercise	Increased training volume	↑	May indicate increased training stress and possibly inadequate recovery

sensitivity [167]. Our recent study demonstrated that acute negative energy balance induced via prolonged rowing training with an estimated energy expenditure of 1200 to 1500 kcal elicited a decrease in visfatin after 30 minutes postexercise [168]. Postexercise visfatin was also related to the distance covered [168]. Another study suggested that the ghrelin to obestatin ratio could be used to describe energy homeostasis [169]. Specifically, obestatin, a recently discovered peptide that is similar to ghrelin and is produced by the endocrine cells in the gastrointestinal tract, has the opposite effect to ghrelin on food intake [169]. The ghrelin to obestatin ratio could be used to monitor energy balance in athletes during weight reduction periods and also in training periods of high energy expenditure to minimize the effect of possible negative energy balance. Understanding the exact regulatory roles of the peripheral signals of energy balance will help us to better understand the complex mechanisms of adaptations to acute exercise and chronic training and to use these peripheral signals as possible markers of training stress.

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