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Obesity, food intake and exercise: Relationship with ghrelin

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Summary

Obesity, a disorder of body composition, is defined by a relative or absolute excess of body fat. In general adult population, obesity has been associated with a diverse array of adverse health outcomes, including major causes of death such as cancer, diabetes, cardiovascular disease, as well as functional impairment from problems such as osteoarthritis and sleep apnea. Ghrelin is a newly discovered peptide hormone which plays an important role in obesity. It is a powerful, endogenous orexigenic peptide and has a crucial function in appetite regulation, as well as short – and long-term energy homeostasis. In the presence of increased obesity, decreased physical activity, and high food consumption, the relationship between exercise, appetite, food intake and ghrelin levels has important implications. In this review, we discuss the effect of acute and chronic exercise performance on appetite, food intake and ghrelin and their relationships.

Keywords: Exercise – Apettite – Food intake – Ghrelin

Introduction

Overweight and obesity can be defined as abnormal or excessive fat accumulation that may impair health. In the general adult population, obesity has been associated with a diverse array of adverse health outcomes, including major causes of death such as cancer, diabetes, cardiovascular disease, as well as functional impairment from problems such as osteoarthritis and sleep apnea [1]. Obesity has been increasing rapidly throughout the world, and the incidence of worldwide obesity has more than doubled since 1980. In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese. The most common causes of obesity are overeating and physical inactivity. (http://www.who.int/mediacentre/factsheets/fs311/en/)

As a growing number of people suffer from obesity, understanding the mechanisms by which various hormones and neurotransmitters have influence on energy balance has been a subject of intensive research. However, the manner in how hormonal systems contribute to the development or maintenance of obesity is as yet not very clear.

Ghrelin, is a 28-aminoacid hormone which strongly affects the release of growth hormone endogenously, and plays role in the regulation of energy balance and food intake [2]. It is released primarily by ghrelin cells, like X/A cells that exist in the oxyntic glands of the stomach to blood circulation but it is also released from many other parts of the body in smaller amounts [25]. Ghrelin exists in circulation in two forms: acyl, and des-acyl. Acyl ghrelin is thought to be more involved in appetite regulation. Ghrelin exerts its effects by stimulating arcuate nucleus neurons that co-express the Neuropeptide-Y (NPY) and Agulated Related Peptid (AgRP) orexigenic peptides [43].

Ghrelin was first discovered as an endogenous ligand for the receptor that causes growth hormone release (GHS-R), and later studies have revealed that it strongly stimulates food intake accretion of body mass [42, 80]. Because of these effects, later studies have focused on the effects of ghrelin on energy homeostasis.

In the experiments conducted on animal and human subjects, centrally or peripherally injection of ghrelin, continuously or over repetitive periods, caused increase in weight, by causing increase in food intake, and decrease in energy expenditure [5, 61, 80, 88]. Blocking of endogenous ghrelin stimulation via various methods causes decrease in food-intake, and gaining weight [4, 6, 60, 75, 80].

Many studies have been conducted recently on the regulation of bioactivities of orexigenic factors such as ghrelin, in order to use in the treatment of obesity. Bistable RNA-based compounds that are created in vitro and can

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be related to acyl-ghrelin successfully inhibited ghrelin mediated GHSR (growth hormone secretagogue receptor) activation on animal subjects [73]. In addition, ghrelin immunoconjugat injection decreased nutrition efficiency and body weight gaining, and also decreased the percentage of body fat among rats [90].

Ghrelin is associated with obesity in two ways: first, it has short-term effects on hunger to stimulate eating (causing more food intake), and; second, it has longer-term effects on the control of energy balance. Another possible application of the kinetic effects of ghrelin is based on the finding that gastric discharge is faster among clinical obese patients than normal individuals [84]. The reason for gastric discharge being faster among obese is that post-prandial ghrelin levels decrease less than in normal individuals [44]. This situation among obese contributes to the increase in food intake. Ghrelin antagonists may be used to delay gastric discharge among obese. In this way, individuals feel satiated for longer and thus consume less food. From these perspectives, ghrelin physiology could be possibly used to stimulate long-term and continuous weight loss. Sherman et al. [72] tested the effect of synthetic oligonucleotide (spiegelmer) that neutralizes the effect of ghrelin by binding to it, on obese rats fattened via diet. Research findings revealed that body weight, food intake and fat storage decreased on oligonucleotide injected rats compared to the control group. Another study found that GHSR antagonists decreased nutrition among lean and obese rats fattened via diet [4]. Peripheral provision of these antagonists decreases gastric discharge speed, and thus protracts a sense of satiety leading to a decrease in food intake. Clinical application of these methods doesn't seem likely in the near future. However, the fact that appetite/energy balance regulation can be controlled with ghrelin is promising.

Ghrelin antagonists won't have a major effect on the loss of body-weight as the basic ghrelin level is already low among obese individuals. However, ghrelin increases caused by the adaptive physiological mechanism to regain the lost weight, can be prevented with ghrelin blocker agents, and so weight maintenance will be easier [20]. In addition, studies conducted on animal subjects have revealed that, after body weight loss, not only the ghrelin level in the circulation, but also the ghrelin receptor expression in the hypothalamus increase [81]. Besides, orexigenic activity sensitivity of ghrelin also increases [65]. All these findings suggest that anti-ghrelin pharmaco-therapeutics may help in body weight maintenance.

Exercise is a non-pharmacological method used by itself or in combination with food-intake restriction in obesity treatment and body weight control [24, 59]. During exercise, a negative energy balance occurs depending on the intensity and duration of the exercise, and this negative energy balance affects appetite and food-intake to a great extent (Powers and Howley, 2002). The most important hormones that can explain the effect of exercise on appetite and food intake is ghrelin. Therefore, understanding the effects of exercise and food-intake limitation on appetite, food-intake and on ghrelin is very important in terms of obesity aetiology, and its potential treatment. Concordantly, the purpose of the present review is to reveal the effects of exercise on ghrelin, appetite and food intake and their relationships with obesity in the light of current information.

The Effect of Acute Exercise on Appetite, Food Intake, and Energy Balance

Many short-term exercise studies have been conducted to determine the effect of acute exercise on food intake and sense of hunger. While findings of these studies are sometimes contradictory, most have reported that low and moderate intensity exercises either increased or had no effect on hunger and food intake [15, 69, 76, 83]. Interestingly, studies conducted with high intensity exercise reported that acute intense exercise suppressed hunger and energy intake [17, 37, 85]. Unlike low and moderate intensity short-term exercise, high intensity short-term exercise generally induced short-term negative energy balance and were found to suppress hunger; which supports the perspective that exercise induces anorexia. Suppression of hunger is a short-term state and has no distinctive effect on energy intake. Many studies, which were conducted with exercise and open-buffet, reported that acute exercise didn't change total food intake [38, 39].

Some studies could not report the effect of acute exercise on energy balance because they didn't take the energy expenditure due to exercise into consideration [41, 52]. There may be an increase in absolute (total) energy intake after exercise, but decrease in relative energy gain (absolute energy – energy expenditure during exercise) shows that exercise provides a short-term negative energy balance. Consequently, moderate and low intensity acute exercise increases or does not affect hunger. Suppression of hunger only occurs during high intensity acute aerobic exercise (>60% VO_{2max}) and only for a very short period of time post-exercise, and cannot be observed after low and moderate intensity exercise [17, 37, 85]. The possible reason for the suppression of hunger only after high intensity exercises is that the activation of sympathetic nervous system increased during high intensity exercise, blood flow in splanchnic area decreased and most of the blood in the circulation is directed to active muscles [23, 33].

The Effect of Chronic Exercise on Energy Intake, Energy Balance, and Body Weight

Despite its effect on short-term weight loss, the role of food restriction in long-term weight loss is disputable. According to the findings of 31 comprehensive recent

researches that examined the effect of long-term food limitation of weight loss, even a 5–10% weight loss was observed in the first 6 months, 1/3–2/3 of the subjects gained more weight than they lost in the following 4–5 years [49]. Recent research conducted on 22 sedentary obese subjects reported that 12-week (exercise done five days a week, and at 75% of the heart beat rate) weight-loss program decreased body weight, while it increased hunger insulin level, acyl ghrelin level, and sense of hunger [50]. According to the findings of this research, long-term exercise decreased body weight, but a regulating physiological mechanism resists weight-loss by increasing sense of hunger and acyl ghrelin. The issue in long term weight loss may not be with food limitation; but it maybe mostly with an inability for individuals to sustain the limitation along with a corresponding reduction in BMR (Basal Metabolic Rate) and perhaps NEAT (Non-exercise activity thermogenesis) [45].

Behavioural mechanisms are probably more effective than physiological and metabolic mechanisms in re-creating the energy balance impaired with exercise [15, 30]. Energy balance impaired with exercise can be reversed by two major behavioural mechanisms: an increase in energy intake and/or decrease in spontaneous non-exercise energy expenditure [13, 67, 87]. Increase in energy intake after exercise is possibly resulted from the increase of appetite and over-free diet including high energy food. The reason for not being careful with the food taken after exercise is the thought that with the energy expenditure during exercise, the extra energy taken can be compensated [32].

Research is conflicting as to the effect of exercise on body weight: some studies report that chronic exercise decreases body weight, others report no significant change, and some even show weight gain. When taken as a whole, the common conception is that exercise is not an effective strategy to promote weight loss [66, 68]. The relative ineffectuality of exercise on body weight loss is multifactorial. For one, body fat mass decreases with exercise, while fat-free mass increases. Despite the improvement in body composition, generally there is no net weight loss [14]. Moreover, many physiological and behavioural regulating mechanisms are activated to re-set the energy balance impaired with exercise. Specifically, a phenomenon called adaptive thermogenesis causes a decrease in basal metabolic rate (BMR) to counteract weight loss [31]. Additionally, improvements in maximal oxygen consumption (VO_{2max}) and running economy occurs with long-term exercise, resulting in a decreased energy expenditure at the same level of exercise intensity compared to before initiation of an exercise program. Consequently, exercise programs for weight-loss decrease body weight; and also energy amounts consumed during exercise and recovery. The combination of these factors helps to explain why the rate of weight loss is high at the beginning of a weight-loss program and subsequently decreases over time.

The inconsistencies between research findings on chronic exercise and food restriction may be the result of methodological differences such as the content of the diet; type, intensity, duration, and frequency of exercise; and individual differences such as reactions to exercise, energy intake, and energy expenditure. Many studies have examined the effect of chronic exercise on energy balance without controlling or directly measuring energy intake and expenditure [9, 26, 56]. Additionally, the increase in energy expenditure stimulated by exercise is based on the assumption that normal activity during the day increases or doesn't change [27, 55]. Body weight was found to be decreased in controlled studies in which energy intake is fixed or adapted according to exercise [31]. Moreover, a current review found that exercise has important effects in body weight control and attenuating re-gain of the lost weight [10]. For this reason, exercise should be included in long-term weight control or weight loss programs, and thereafter adopted as a life style.

Ghrelin Response to Acute Exercise and Appetite and Food Intake Relation

Ghrelin is one of the possible factors that can explain the change in food intake during exercise. However, the effect of acute exercise on total ghrelin is quite disputable in the studies conducted so far. A majority of studies found that ghrelin levels didn't change after exercise, [21, 22, 40] while some other studies reported an increase or decrease in ghrelin levels [12, 19, 53]. Research by Stokes et al. [77, 78]found that total ghrelin decreased after exercise. The difference between Stokes et al. studies and other studies on the topic was that the other studies were conducted with using lactic acid and aerobic energy systems but the studies conducted by Stokes et al. were completely based on alactacid anaerobic energy system, short-term and high intensity exercises.

Total ghrelin levels increased after moderate intensity aerobic exercise, but did not increase after high intensity exercise. Moreover, the increase in plasma total ghrelin level was not parallel with the change in sense of hunger [24]. Sense of hunger was suppressed during and after exercise, but plasma total ghrelin concentration didn't change [18]. Ueda et al. reported that 60min. cycling exercise performed at 50% of VO_{2max} decreased food intake and relative food intake among both obese and healthy young men, but this decrease was unrelated to ghrelin [82]. Martins et al. [51] examined the effect of 60min. cycling exercise performed at 65% of maximal heart beat rate on ghrelin, sense of hunger, and food intake. According to the findings of this study, moderate intensity acute exercise decreased sense of hunger temporarily, and this temporary decrease contributed to

the short-term negative energy balance. However, this temporary effect on appetite could not be explained by the change in ghrelin levels. Ballard et al. [8] stated that 80 minute resistance exercise decreased plasma ghrelin concentration among 21 young men, but there was no correlation between ghrelin concentration and subjective hunger score. The findings of this research indicates that sense of hunger during and after acute exercise was not related to total ghrelin concentrations.

Research shows that high intensity exercises suppresses appetite but this suppression is not associated with a decrease in total ghrelin concentration. Many studies on ghrelin examined only total ghrelin as there were only total ghrelin kits on the market at the time. The ability to measure acyl ghrelin (AC) that is named as active ghrelin because it can connect to GHSR-1 biologically, and des-acyl ghrelin (DG) named as inactive because it cannot connect to GHSR-1, has just recently become available. Therefore, most of the studies conducted on exercise to date have examined how exercise affects total ghrelin. There have been only a few studies that examined the effects of exercise on acyl and des-acyl ghrelin, but acylation of ghrelin is necessary for appetite regulation [7, 17, 34-37, 47, 64, 85]. Acyl ghrelin and appetite increased after 1-hour aerobic exercise on 5 sequential days in normal weight and obese adolescents but total ghrelin did not change (Kim et al.2008). King et al. [36, 37] found that low and high intensity exercise done for 60 minutes and more did not affect hunger, food intake, and acyl ghrelin. On the contrary, Ozen et al. [64] reported that low intensity 60 minute treadmill exercise done at 50% of VO_{2max} increased acyl ghrelin among young healthy men. Vatansever-Ozen et al. [85] reported that 15 minutes high intensity exercise (70% of VO_{2max}) done immediately after 105 minute low intensity exercise (50% of VO_{2max}) suppressed acyl ghrelin and hunger. Similarly, Broom et al. [17] found in their study conducted on healthy male that high intensity aerobic and resistance exercises suppressed AG and hunger. These findings show that acyl ghrelin may be affected differently from exercise intensity.

The effect of exercise on food intake not only depends on exercise intensity but also on gender and body composition [29, 71]. Sartorio et al. [71] found that GRH increased after 60-90 min. exercise done at 80% of VO_{2max} both in female and male athletes, while ghrelin increased only in male athletes. This finding indicates that ghrelin release during exercise is different between males and females. Some recent studies have shown that ambient temperature may change the effect of exercise on food intake. The low temperature of the environment in which the exercise is done or bathing with water colder than body temperature after exercise affects food intake significantly. High environment temperature after exercise suppressed food intake, while food intake increased after exercise done in cold water [29, 74, 86]. The mechanism of the correlation between temperature and food intake has yet to be fully elucidated, but it is commonly thought that appetite hormones can be effective in the regulation of internal temperature.

It is assumed that only acyl ghrelin is effective in regulation of food intake and appetite because it can connect to GHSR-1. However, recent studies have revealed that unlike acyl ghrelin, des-acyl ghrelin can activate different unidentified receptors and thus stimulate different physiological and metabolic effects [3, 16, 79]. Previous research reported that des-acyl ghrelin decreased food intake and stimulated negative energy balance by delaying gastric discharge [3]. Kim et al. [34] reported that body weight, BMI, and body fat percentage decreased in obese children after 12-week resistance and aerobic exercise, while total ghrelin increased at 30.4%, des-acyl ghrelin increased at 31.9%, and acyl ghrelin did not change. There is a strong correlation between decrease in body weight and body fat and the increase in des-acyl after exercise in obese children [54]. Consequently, acyl and des-acyl ghrelin levels should be measured separately for a better understanding of their different roles.

Ghrelin Response to Chronic Exercise and Appetite and Food Intake Relation

Exercise is an essential part of weight control and it is used with food restriction. Studies conducted on obese and healthy individuals stated that ghrelin levels increased with weight loss after exercise and food restriction.

Moraes et al. [58] reported that acyl-ghrelin increased after a six month of resistance exercises in hemodialysis patients. Martins et al. [50] reported that body weight decreased while acyl ghrelin and appetite increased after 12-week exercise (75% of HR, 3days/week) program in 22 sedentary and obese women. Similarly, Santoso et al. [70] reported that body weight decreased while ghrelin increased at 21.2% after a 6-month weight-loss program including diet and exercise in 35 hyperlipidemic women. Zahorska et al. [89] reported an average 8.7 kg weight loss, decrease in BMI and body fat percentage, along with increase in ghrelin after a 3-month weight-loss program (diet + exercise) among obese women. Research on obese women conducted by Mizia-Stec et al. [57] found an increase in serum ghrelin after a 3-month weight-loss program. These studies also discussed that weight-loss among obese women decreased blood pressure significantly, and this decrease was realized with a ghrelin related mechanism. Maestu et al. [48] reported a significant decrease in body weight, BMI, and body fat percentage among 14 bodybuilders (7 competition, 7 control) who increased training volume and decreased food intake in order to decrease body fat percentage 13 weeks before

participating in the national championship. In addition, they reported an increase in plasma ghrelin 5 weeks (20.4%), and 3 days (6%) before the competition. Additionally, body weight, body fat percentage, and sense of satiety decreased, and serum total ghrelin level increased among non-obese sedentary women after a 3-month diet and exercise program [46]. These findings indicate that ghrelin is a metabolic stimulant that plays a key role in the system that shows there is energy deficit, and it is effective in meeting the possible energy deficit in this system.

Contrary to the above findings, Benso et al. [11] reported a significant decrease in body weight, but no change in leptin and ghrelin among 9 elite mountaineers after a 7-week climb on Mount Everest. Nonetheless, after high altitude climbing, GRH, and IGF-1, and insulin-like growth factor binding protein (IGFBP-3) increased [62]. Ozcan et al. [63] reported that sixteen weeks of exercise caused a significant decrease in body weight and fat mass but had no effect on ghrelin levels in sedentary women.

As can be understood from the findings of the above studies, recent research on adults and children have shown that weight loss increases circulating ghrelin levels. Even though the mechanism by which weight loss increases circulating ghrelin is not well understood, it is assumed that positive energy balance is stimulated due to 3 mechanisms. First; the decrease in fat utilization independently from GRH, and increase in carbohydrate utilization. Second; the anabolic effect, caused by the increase in GRH and IGF-1 production. And third; the stimulation of long-term food intake via possibly neuropeptide-Y (NPY) [28].

Nitsche et al. [62] reported that BMI decreased after 10-day calorie limitation and exercise among obese children and adolescents, ghrelin increased with respiratory quotient (RQ); and these two are interrelated. This shows that ghrelin is a sensitive indicator of change in substrate oxidation. As RQ levels increase, fats use decreases, and carbohydrate use increases. In other words, as body weight decreases, ghrelin levels increase, and carbohydrate use increases in order to preserve fat storages. In addition, ghrelin activates NPY/AgRP neurones in arcuate nucleus, and stimulates food intake [61]. Ghrelin increase among obese individuals after weight loss is possibly a physiological protection mechanism activated in order to regain the lost weight (with negative energy balance) with positive energy balance.

Conclusion

Findings of the current studies on acute and chronic exercise conducted on human subjects that examined the effect of exercise on hunger, food intake and ghrelin are generally inconclusive. Some of these discrepancies in these findings may have resulted from differences between intensity, duration, and type of the exercise, or different research designs such as time of food intake and differences in characteristics of subjects.

For this reason, many more studies using various subject groups (active, inactive, obese, non-obese etc.) and different methods (duration, intensity, and context of exercise, time of taken blood samples etc.) are required in the future. Studies conducted up to now provide these findings; 1) low and moderate intensity short-term exercises do not affect hunger, food intake, and ghrelin, while high intensity exercises decrease hunger and food intake, and this decrease is related to acyl ghrelin, 2) chronic exercise along with food intake control contribute to weight-control and weight-loss.

However, reductions in body mass associated with weight-loss programs increases sense of hunger and ghrelin via a regulation mechanism and results in re-gain of the lost weight. In light of this information, individuals should continue exercise programs with a re-arrangement of intensity, duration and extents in order to maintain loss weight, and adopt regular exercise as a life style.

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