Brain science of exercise-eating linkage for improvements in modern human health

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Abstract The health values of exercise and eating are separately established as two independent pillars for human life. However, a substantial amount of evidence shows the physiological crosstalk by which exercise might be associated with hunger and satiety, as regulated by gut hormones. A single bout of exercise tends to suppress the blood levels of orexigenic acylated ghrelin (AG) and to increase the levels of anorectic hormones like peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). It was reported that, while sustained physical activity increases the drive to eat in the fasting state, this seems to be compensated by an improved satiety response to a meal through changes in the gut hormone systems. A few studies reported exercise-induced reductions in the neural responses to food-related cues in higher brain center networks involved in the attentional, emotional and cognitive functions. The present review introduces the latest research on the effects of various types of exercise on the neuroendocrine networks related to hunger, satiety, appetite, and responses to food-related cues, suggesting the physiological rationale for the linkage between exercise and eating in humans. Next, the possibilities of the brain science of exercise and eating for improvements in modern human health in various generational groups are discussed.

Keywords : appetite, exercise, gut hormones, brain science

Introduction

Eating and exercise are clearly relevant to health and disease. For example, health maintenance requires proper nutrition on a regular basis. However, the modern lifestyle provides ample opportunities for excessive food intake⁽¹⁾, which often makes it difficult to eat properly⁽²⁾. Another modern health issue is the reduction in food intake that subsequently leads to sarcopenia in elderly persons and malnutrition in young females^(3,4). Here, a key factor that determines eating behavior is appetite^(5,6). Appetite is the desire to eat regardless of one's physiological hunger⁽⁷⁾. A good appetite is generally regarded as a sign of good health, and a decrease in appetite could be an early sign of the progression to worse health⁽⁸⁾. Regarding exercise, scientific evidence has confirmed a wide range of health benefits, including a higher energy expenditure and improved metabolic functioning^(9,10). Additionally, over the past few decades, a considerable amount of research has

demonstrated the roles of exercise in the maintenance and enhancement of various brain functions including cognition, emotion, mood, and motivation⁽¹¹⁻¹⁵⁾.

In general, the health values of eating and exercise are separately established as two independent pillars for human life. However, considering that eating and exercise take place in the body of a single individual, it is plausible that some physiological crosstalk mechanisms might coordinate these two activities. In this light, a substantial amount of evidence shows the physiological interactions by which exercise might be associated with hunger and satiety, as regulated by gut hormones, in both healthy individuals and patients with metabolic diseases^(16,17). In addition, some studies investigated the roles of exercise in the appetitive responses of the higher brain centers in association with cognitive and emotional functions^(18,19).

The present review introduces the latest research on the effects of various types of exercise on the neuroendocrine networks related to hunger, satiety, appetite, and responses to food-related cues, suggesting the physiological rationale for the link between eating and exercise in hu-

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mans. Next, the possibilities of the brain science of eating and exercise for improvements in modern human health are discussed.

Effects of various types of exercise on the neuroendocrine networks related to hunger, satiety, appetite, and responses to food-related cues

Hunger and satiety are largely regulated by the autonomic and hormonal networks that connect the peripheral gastrointestinal tract and the feeding and satiety centers of the hypothalamus. Network mediators include ghrelin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1)²⁰⁻²⁵. First, we present the physiological effect of exercise on these hormones.

Ghrelin is predominantly synthesized by the oxyntic cells in the stomach in response to fasting. Ghrelin administration has been shown to increase the number of meals eaten without causing significant changes in meal size, thereby resulting in weight gain. Total ghrelin is classified into two categories: orexigenic acylated ghrelin (AG) and anorectic desacyl ghrelin (DG). Recent research indicates that various types of exercise induce significant changes in the AG blood levels²⁶. AG is suppressed during running and resistance exercise²⁷⁻²⁹. Exercise intensity and duration are determinants of the AG response to acute exercise³⁰. For example, AG is suppressed by rope skipping (295 ± 40 kcal; three 10-minute sets performed at 5-minute intervals), similar to using a bicycle ergometer (288 ± 36 kcal; three 10-minute sets at 5-minute intervals)³¹. In addition, AG was previously shown to be suppressed during swimming³². In our preliminary study, AG was significantly lower when walking in water (oxygen uptake = 1.64 ± 0.12 L/minute over 60 minutes) than on land (oxygen uptake = 1.67 ± 0.11 L/minute over 60 minutes) (unpublished data).

In contrast, most of the other gut hormones generally suppress food intake. The precursor form, PYY₁₋₃₆, is known to be secreted postprandially into circulation by the L cells, which are located mainly in the distal ileum and colon, and rapidly metabolized by dipeptidyl peptidase IV, an enzyme that results in its conversion to PYY₃₋₃₆. PYY₃₋₃₆ is a more potent suppressor of food intake than its precursor, PYY₁₋₃₆. GLP-1, a product of the preproglucagon gene, is activated by post-transcriptional processing of the N-terminus cleavage and released from intestinal L cells in response to ingesting nutrients. Degradation of the active form of GLP-1 in the circulation is caused by a similar truncation of the N-terminus of the molecule, resulting in the inactive form. Most studies report increases in the blood levels of these gut hormones in individuals following a single bout of exercise compared with individuals in the pre-exercise or resting condition²⁶. We reported the association between the exercise-induced increase in plasma GLP-1 and decreased food intake after a single bout of exercise³³. In addition, it is

likely that, whereas changes in orexigenic AG levels are influenced by exercise intensity, changes in the anorectic PYY and GLP-1 levels depend on the volume of exercise and energy expenditure³⁴. The mechanisms responsible for changing these hormones are unknown, but some potential mechanisms have been proposed: 1) blood flow redistribution; 2) sympathetic nervous system activity; 3) gastrointestinal motility; 4) interleukin-6; 5) blood concentrations of free fatty acids, glucose and insulin; 6) lactate production; and 7) body temperature³⁴. In addition, we also investigated the neural regulation of GLP-1 and PYY secretion during exercise in rats using a hindlimb muscle contraction model. The increases observed in the plasma GLP-1 and PYY levels following exercise were mediated by the activation of skeletal muscle-derived afferent neurons, not by mechanisms through the neural pathway of the vagus nerve³⁵.

Previously published studies investigated changes in the blood levels of gut hormones during sustained physical activity in both healthy and obese individuals. For instance, an intervention study on a 12-week supervised exercise program (exercise performed 5 days/week with a 500-kcal energy deficit per session at 75% of the participant's maximal heart rate) conducted on 22 middle-aged, sedentary, overweight or obese individuals reported that exercise induced significant weight loss, whereas the fasting hunger sensation and plasma AG levels at the end of intervention were higher than before intervention³⁶. Additionally, the intervention caused a postprandial suppression of plasma AG as well as a postprandial increase in GLP-1. We also reported the effects of 12 weeks of exercise training on gut hormone levels after a single bout of exercise in middle-aged women³⁷. The incremental responses of blood GLP-1 and PYY after a single bout of exercise were enhanced after the 12-week exercise training. These results indicate that, whereas sustained physical activity induced an increase in the drive to eat in the fasting state, this seems to be balanced by an improved satiety response to a meal in the gut hormone system. As described above, the effects of age and gender on the exercise-induced kinetics of gut hormones remain to be fully elucidated.

While crosstalk between peripheral hormonal players and the hypothalamus has been thought as a possible explanation for the differences in food consumption between before and after exercise, only a few studies have investigated whether acute and chronic exercise can also affect the brain networks involved in the emotional and cognitive processing of food-related cues. An initiative study by Cornier et al. investigated the effects of 6 months of exercise intervention on the neural responses to food-related cues in obese or overweight individuals using functional magnetic resonance imaging (fMRI)¹⁸. The supervised exercise program was designed to target an increase of 2,500 kcal/week, and the neural responses to visual food cues were compared between pre- and post-

exercise intervention. This study reported a significant attenuation in the neuronal response to visual food-related cues, primarily in the network of brain regions known to be important to attention and motivation, and of particular note is a positive association of the reduction in the insula responses to food-related cues with a loss of fat/body mass and a change in the blood leptin concentration, though the intervention did not impact any of the measures of appetitive behaviors. A similar fMRI study by Evero et al. reported that a single 1-hour bout of cycling at 83% of maximal heart rate attenuated the neural response to food pictures in some brain areas involved in visual processing, attention and motivation when compared to control images. The observed reductions in the neural responses suggest that the attentional response to visual food-related cues could be reduced with a single bout of aerobic exercise, possibly contributing to the indirect effects of physical activity on appetite. However, it remains unclear whether these attenuated neural responses contribute to an actual suppression of energy intake¹⁹⁾.

Other types of studies with electroencephalography assessed exercise-induced alterations in neural responses by measuring the event-related potentials (ERPs) triggered by visual food-related cues before and after exercise intervention. In contrast with fMRI, this approach is sensitive to real-time neural processes and can be decomposed into a number of components on the time scale of milliseconds, which reflect different stages of information processing. These studies took particular note of the impact of a single bout of exercise on the attentional response to visual food-related cues. Hanlon et al. reported that the amplitude of the specific ERP component in response to visual food cues - the late positive potential used to index food motivation - was reduced by moderate-to-vigorous exercise on a treadmill (3.8 mph at a 0% grade for 45 consecutive minutes) in both obese and lean women³⁸⁾. However, there were no significant differences in subjective food motivation triggered by visual food cues or energy/macronutrient intake recorded 24 hours after the exercise session compared to the non-exercise session. A more recent study by Fearnbach et al. examined whether neural responses to food-related cues are modulated by acute exercise in obese adolescents³⁹⁾. In the exercise session (65% of maximal oxygen uptake for 45 minutes), a significant reduction in the amplitude of P3b - a specific ERP component that reflects the level of cognitive engagement in the processing of food cues - was observed compared to non-food cues. Both absolute and relative energy intake were significantly reduced after exercise, whereas the self-reported appetite remained unchanged. Overall, the association between exercise-induced reductions in the neural responses to food-related cues and changes in subjective appetite and food intake require further careful studies (Table 1).

The brain science behind the linkage between exercise and eating for human health

In humans, eating behavior is not only determined by hunger, the feeling of satiety, and energy shortage, but also by complex factors including sensory, attentional, emotional, and cognitive aspects⁴⁰⁾. For example, there are preference and memory for food, emotions such as depression and irritation, psychological stress, fatigue, and individual belief (cognition) about foods that “I am hungry because I exercised” and “I do not want to leave food”. Importantly, motivation is required when transitioning from desire (appetite) to action (eating behavior) (Fig. 1)⁴¹⁾. The hypothalamus and gastrointestinal hormones are known to be responsible for hunger and feelings of satiety; and the majority of evidence regarding the association between exercise and appetite is related to the exercise-induced dynamics of gastrointestinal hormones in the blood. However, one’s actual eating behavior is largely dominated by the motivational process in response to circumstances such as the presence of food-related cues and food availability. Our previous studies reported that, under experimental conditions where the participants were motivated to eat, an instantaneous neural response occurred in the insular cortex and the intensity of the response was positively associated with self-awareness of the appetitive motives in one’s everyday diet^{42,43)}. This observation is consistent with evidence that, in eating behavior, the insular cortex is a critical platform that integrates 1) interoceptive states based on information from the sensory nerves into conscious feelings and 2) decision-making processes that involve uncertain risks and rewards⁴⁴⁾. In addition, the insular cortex plays an important role in the emotional brain network in determining human behavior in association with cognitive brain function^{45,46)}, and these brain regions are members of the cerebral autonomic network⁴⁷⁻⁴⁹⁾. Given these functions of the insular cortex, it is interesting that, as shown in previous studies by Cornier et al and Evero et al.^{37,38)}, the neural response to visual food cues in the insular cortex is attenuated after a single bout or continuous exercise intervention. Besides, other brain regions like the prefrontal cortex are known to play roles in increasing or decreasing appetite and motivation to eat⁴³⁾, and brain activities related to exercise-induced physical stress or fatigue could modify appetite and eating behaviors. Furthermore, it should be kept in mind that the movement of the body induces peripheral dynamic changes such as hemodynamic and metabolic changes, myokine release, and muscle inflammation, which appear to be transmitted and integrated in the brain. Such peripheral information might affect the emotional and cognitive brain circuitry that regulates appetite and motivation to eat. Accordingly, assessing the spatiotemporal dynamics of the whole-brain circuitry is required to obtain a more comprehensive understanding of the association between exercise, appetite, and motivation to eat.

Table 1. Studies on the roles of exercise in the appetitive responses of the higher brain centers in association with cognitive and emotional functions.

Participant			Exercise protocol				Stimulation and measurements			
<i>n</i> (M/F)	Age	Body type	Type		Duration and frequency	Amount	Dietary preload	Interval after exercise	Food-related stimuli (pictures)	Brain function
12 (7/5)	Middle age	Obese	Repeated	Treadmill	5 days/wk x 6 mos	Progressive exercise intervention Target workloads (500 kcal/day at 75% of VO ₂ max)	NA	NA	Hedonic foods (vs. vs. non-food object)	f-MRI
30 (17/13)	Young adult	Habitually active and non-obese	Single	Ergometer	60 min	Constant load at 83 ± 1.0 % of maximal heart rate (power output, 140 ± 6.9 W)	No	168 ± 9 sec	High- or low-energy food (vs. non-food object)	f-MRI
35 (0/35)	Middle age	Obese or nonobese	Single	Treadmill	45 min	Constant load at 3.8 mph, 0% grade	Yes	within 1 hr	Food or flower	EEG (LPP component of ERP)
19 (19/0)	Adolescent	Obese	Single	Ergometer	45 min	Constant load at 65% VO ₂ max	Yes	15 min	Food and non-food objects	EEG (P3b) with odd ball task with food pictures

↓, decrease; ↑, increase; →, no change.

EEG, electroencephalography; f-MRI, functional magnetic resonance imaging; LPP, late positive potential; NA, not applicable; OFC, orbitofrontal cortex; mph, mile per hour; VO₂max = maximal oxygen intake.

LPP, the late positive potential; ERP, event-related potential; P3b, event-related component reflecting the level of cognitive engagement in the processing of food cues.

M, male; F, female.

Fig. 1 Appetite, motivation to eat and eating behavior.

Human eating behavior depends not only on hunger and satiety but also on emotional and cognitive factors which determine motivation to eat.

The association of exercise with appetite and motivation to eat appears to prove the real value of exercise intervention not simply as a means for energy expenditure. This point is important for resolving the concerns of our time about food and health. For instance, many of middle-aged persons who are exposed to stress and an abundance of food tend to become obese or subsequently develop lifestyle diseases. Many young women desire to be slim, resulting in undernutrition in association with systemic illnesses like disturbances in growth and impairments in bone health⁴. Many elderly people with declines in oral and cognitive functions often eat less, and in turn suffer from frailty and chronic diseases³. These people appear to have dysfunctional balancing mechanisms in their brain

circuitry that induce or inhibit appetite and motivation to eat. For the development of useful interventions as a strategy for lifestyle modification, the effects of exercise on these dietary characteristics should be taken into account in each generational group, and the physiological connection between eating and exercise deserves more attention. Such efforts will possibly lead to the development of novel and comprehensive solutions to the health problems in today's society.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Results					Reference
Appetitive scale	Energy intake	Weight	Brain function	Others	
→	↓ (self-reported)	↓ (fat mass)	↓ Brain regions for attention, visual processing and motivation including left insula, bil. parietal cortex, visual cortex)	Change in body weight and fat mass with chronic exercise correlated with change in insula response	[Cornier MA, et al., 2012]
↓	(not measured)	NA	↓ Food reward regions including insula, putamen, rolandic operculum, OFC)	No significant correlations between neural responses and subjective appetite	[Evero N, et al., 2012]
-	→ (weighed food records for 24hrs)	NA	↓ LPP amplitude waveforms in response to food stimuli, independent of BMI category	No significant correlations of neural responses with subjective valence (pleasant) and emotion (excited) and with energy intake 24 hr after exercise	[Hanlon B, et al., 2012]
→	↓ (ad libitum 30 min after exercise)	NA	↓ P3b amplitude in response to food stimuli	NA	[Feambach SN, et al., 2016]

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