The Role of Physical Exercise in Food Intake Suppression

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Abstract

Obesity is a global health issue since it is related to diseases that are the leading causes of mortality, such as diabetes, stroke, and cardiovascular disease. A long-term imbalance between energy intake and energy expenditure is one of the factors contributing to obesity. In addition to increasing energy expenditure, physical exercise can also aid in weight loss by decreasing food intake. An increase in appetite-regulating hormones (ghrelin, GLP-1, leptin, and adiponectin), myokines (IL-6 and irisin), and lactate mediates the suppression of food intake during physical exercise. These substances function as signals that regulate food intake at the peripheral and/or central nervous system levels. Peripherally, lactate inhibits ghrelin secretion, while IL-6 increases GLP-1 secretion. In the center for regulating food intake, lactate, IL-6, leptin, and adiponectin act by inhibiting the release of orexigenic neuropeptides (NPY/AgRP) and increasing the release of anorexigenic neuropeptides (POMC). This review highlighted the role of physical exercise in overcoming obesity through suppression of food intake mediated by hormones and myokine changes that play a role in regulating food intake either in the periphery or directly in the central nervous system.

Keywords—Physical Exercise, Food Intake, Orexigenic, Anorexigenic

Abstrak

Obesitas merupakan salah satu masalah kesehatan penting di dunia karena berhubungan dengan penyakit-penyakit yang menjadi penyebab utama kematian di dunia seperti diabetes melitus, stroke, dan penyakit kardiovaskular. Ketidakseimbangan antara asupan energi dan penggunaan energi dalam jangka waktu panjang menjadi salah satu penyebab terjadinya obesitas. Selain melalui peningkatan penggunaan energi, latihan fisik juga dapat menurunkan berat badan melalui penekanan asupan makanan yang akan mengurangi energi yang masuk ke dalam tubuh. Peningkatan hormon yang mengatur nafsu makan (ghrelin, GLP-1, leptin, dan adiponectin), miokin (IL-6 dan irisin), dan laktat memperantarai penurunan asupan makanan selama latihan fisik. Zat-zat tersebut berperan sebagai sinyal yang meregulasi asupan makanan di perifer atau di sistem saraf pusat. Di perifer, laktat menghambat sekresi ghrelin sedangkan IL-6 meningkatkan sekresi GLP-1. Di pusat pengaturan asupan makanan, laktat, IL-6, leptin, dan adiponectin bekerja dengan menghambat pelepasan neuropeptida oreksigenik yaitu NPY/AgRP serta meningkatkan pelepasan neuropeptida anoreksigenik yaitu POMC. Review artikel ini membahas mengenai peranan latihan fisik dalam mengatasi obesitas melalui efek penekanan asupan makanan yang diperantarai oleh perubahan dari hormon-hormon dan miokin yang berperan dalam meregulasi asupan makanan di perifer ataupun secara langsung di sistem saraf pusat.

Kata kunci — Asupan Makanan, Latihan Fisik, Oreksigenik, Anoreksigenik

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I. INTRODUCTION

Obesity is one of the health issues that receives global attention because of its negative effects on health. It’s based on the fact that obesity is the main risk factor for diabetes, cardiovascular disease (heart disease and stroke), musculoskeletal disease, and some cancers. These diseases are known as non-communicable diseases (NCDs) and are among the main causes of death in the world. According to the World Health Organization (WHO), obesity is a condition characterized by a body mass index (BMI) of more than 30 kg/m² (BMI ≥ 30 kg/m²). Since 1975, the proportion of the population that is obese has tripled, and it is estimated that around 650 million people in the world were obese in 2016.

Long-term positive energy balance leads to weight gain, which is one of the causes of obesity. Therefore, people with obesity must reduce their weight in order to overcome it. For obese people, the recommended weight loss is 10% of their initial body weight. This can be accomplished by combining behavioral therapy, dietary modification, and physical exercise. Physical exercise can control body weight over the long term because it can be used to establish a negative energy balance by increasing energy expenditure. In addition to increasing energy expenditure, physical exercise can help with weight loss by influencing appetite and food intake. Physical exercise can impact energy balance by influencing the mechanisms that regulate food intake, so it is possible to lose weight through physical exercise.

One of the effects of physical exercise on food intake is “exercise-induced anorexia,” which is caused by an alteration in hormones that regulate food intake, including acylated ghrelin, GLP-1, insulin, leptin, and adiponectin. Changes in these hormones often occur with a decrease in food intake. In addition, lactate and myokines released by contracting skeletal muscle cells during physical exercise also play a role in regulating food intake. Included among these myokines are irisin and IL-6, which can inhibit food intake. These hormones, lactate, and myokines, which are influenced by physical exercise and play a role in controlling food intake, may influence the peripheral or central regulation of food intake.

This article will discuss the importance of physical exercise in the reduction of food intake mediated by hormones and myokine alteration, which regulate food intake either peripherally or directly in the central nervous system.

II. LITERATURE REVIEW

A. ROLE OF THE HYPOTHALAMUS ON FOOD INTAKE REGULATION

The balance between orexigenic signals (stimulating food intake) and anorexigenic signals (inhibiting food intake) influences hypothalamic food regulation. The signal from the periphery will be transmitted to the hypothalamus through the circulatory system or vagal nerve. Then the hypothalamus will communicate with other control centers in the central nervous system and peripheral nervous systems to regulate food intake.

The arcuate nucleus (ARC) is one of the regulatory centers for food intake and energy homeostasis. The ARC is located in the medial basal region of the hypothalamus and plays an important role in the response to satiety, regulation of food consumption, and energy expenditure. Unlike other nuclei in the hypothalamus, the blood-brain barrier (BBB) does not completely protect the ARC. It makes the ARC a prime location for receiving peripheral signals from nutrients and hormones that circulate in the bloodstream.

In the ARC, there are two neuronal groups
that have opposite effects on food intake regulation. The first neuron is found in the medial ARC and releases orexigenic neuropeptides, such as agouti-related protein (AgRP) and neuropeptide Y (NPY). The second one expresses pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), both of which are located in the lateral ARC and have an anorexigenic effect.\(^2,3,12\)

NPY is a neuropeptide that has a similar structure to peptide tyrosine-tyrosine (PPY) and pancreatic polypeptide (PP), which consist of 36-amino-acid peptides. NPY levels depend on the availability of food. The concentration of NPY will increase during the fasting state and decrease during mealtime or immediately after eating. NPY has an orexigenic effect when it binds to its receptor (NPYR1/NPYR5), a G-protein-coupled receptor (GPCR) in the hypothalamus.\(^2\)

AgRP is expressed in the same neurons as NPY in the ARC. In a fasting state and lack of food, increasing ghrelin levels will activate NPY/AgRP neurons. AgRP exerts its orexigenic effect by opposing \(\alpha\)-melanocyte stimulating hormone’s (\(\alpha\)-MSH) influence on melanin-concentrating hormone receptor 4 (MC4R). In addition, AgRP inhibits GABAergic input, which suppresses POMC action potentials.\(^2\)

POMC is expressed on the lateral side of the ARC and will be cleaved with the help of pro-hormone convertase enzymes (PCs) to \(\alpha\)-MSH.\(^2\) POMC is part of the melanocortin system, one of the most important pathways involved in regulating food intake. This system has MC3R and MC4R, which will be bound with \(\alpha\)-MSH and AgRP. POMC will be projected to other parts of the brain and bind to MC4R to induce anorexigenic activity and suppress food intake.\(^2,12\)

**B. Peripheral Hormone and Myokine in Food Intake Regulation**

**Ghrelin**

P/D1 enteroendocrine cells, which are plentiful in the fundus of the stomach, produce and secrete ghrelin, the only digestive hormone that has an orexigenic action.\(^2\) Ghrelin is produced during fasting and decreases following food intake. Ghrelin can enter the brain through the BBB that surrounds the hypothalamus.\(^2,3\) Ghrelin acts through its receptor, growth hormone secretagogue receptor 1\(\alpha\) (GHS-R1\(\alpha\)), which is mostly expressed on NPY/AgRP neurons in the ARC.\(^3\) Ghrelin and its receptor can stimulate food intake by stimulating NPY/AgRP neurons and inhibiting POMC neurons.\(^2,3\)

**Glucagon-Like Peptide 1 (GLP-1)**

The proglucagon gene encodes the digesting peptide GLP-1. Intestinal L cells release GLP-1 in response to the presence of glucose following a meal. GLP-1 functions to provide a satiety signal in order to restrict food intake.\(^2,3,5,13\) GLP-1’s interactions with NPY/AgRP and POMC, as speculated, will induce a feeling of fullness. In addition, GLP-1 decreases food intake by inhibiting gastric emptying.\(^2,14\)

**Leptin**

One of the hormones that regulate hunger and long-term energy homeostasis is leptin.\(^2\) White adipocytes release leptin, with secretion increasing after feeding and decreasing after fasting.\(^2,6,7\) Blood leptin levels are proportional to the amount of body fat. Leptin is able to pass through the BBB and bind to its widely expressed receptor (Ob-Rb receptor) in the hypothalamus. Leptin binding to its receptors (LEPR) inhibits the activity of NPY/AgRP neurons and increases the number of POMC/CART.\(^2,6,12\)
ADIPONECTIN
Adiponectin is a hormone that is produced by adipocytes in both white and brown fat tissue. The function of adiponectin is to regulate glucose and lipid metabolism, as well as promote insulin sensitivity and anti-inflammatory activity. In addition, adiponectin also regulates food intake because adiponectin receptors (ADIPOR 1 or 2) are expressed in the brain mainly by POMC neurons in the hypothalamic ARC. 6

IRISIN
Irisin is a form of myokine produced by skeletal muscle following physical exercise. 6,15,16 Irisin consists of 112 amino acids derived from fibronectin type III domain-containing protein 5 (FNDC5), which is thought to be cleaved by the ADAM family of proteases. 6,16 The secretion of irisin is influenced by a transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), which regulates the FNDC5 gene. 15 After being released by skeletal muscle cells, irisin will enter the bloodstream and cross the BBB to reach the central nervous system. 16 In the central nervous system, irisin induces the synthesis of brain-derived neurotropic factor (BDNF), which can also exert an anorexigenic effect on the central regulation of food intake. 6

INTERLEUKIN-6 (IL-6)
IL-6 is not only known as a proinflammatory agent secreted by adipocytes and macrophages but also as an anti-inflammatory agent that plays a role in regulating metabolic processes. IL-6, as an anti-inflammatory cytokine, is released by skeletal muscle cells during physical exercise, so it is also included in the myokine group. IL-6 secretion by skeletal muscle is affected by the amount of skeletal muscle contraction as well as the duration and intensity of physical exercise. 6 IL-6 can suppress food intake by modulating hormones with anorexigenic effects, such as GLP-1 and PYY. In addition, IL-6 can also act directly on the hypothalamus, suppressing orexigenic neuropeptides and stimulating the release of anorexigenic neuropeptides. 9

LACTATE
One of the conditions that can increase lactate production is during physical exercise, especially high-intensity interval exercise. This is because lactate production depends on the intensity of physical exercise. 9

C. THE ROLE OF PHYSICAL EXERCISE IN SUPPRESSING FOOD INTAKE THROUGH LACTATE AND GHERELIN
Several studies on the effects of physical exercise, such as running or resistance exercise, show a temporary decrease in acylated ghrelin levels after doing that exercise. Although the mechanism remains uncertain, it is believed that lactate contributes to exercise-induced anorexia. Information about the involvement of lactate in exercise-induced anorexia is currently limited to in vitro and in vivo research. 8

Lactate secreted by skeletal muscle cells enters the circulatory system to reach the brain and other peripheral tissues, allowing lactate to reduce food intake both peripherally and directly in the hypothalamus. According to previous studies, lactate can influence the secretion of acylated ghrelin in the periphery, while in the central nervous system it modulates the expression or release of neuropeptides in the hypothalamus and also inhibits ghrelin signaling in the hypothalamus. 8

THE ROLE OF PERIPHERAL LACTATE IN SUPPRESSING FOOD INTAKE
In the periphery, lactate (La) will affect food intake by inhibiting the secretion of the active form of ghrelin, namely acylated ghrelin (AG). Lactate binds to its receptor, known as the G protein-coupled receptor (GPCR81), on enteroendocrine cells and inhibits ghrelin secretion. In addition, lactate
inhibits the activity of the ghrelin O-acyltransferase (GOAT) enzyme, altering ghrelin activation (Figure 1). An in vitro study that stimulated GPCR81 with lactate and showed the suppression of ghrelin production from enteroendocrine cells in the gaster supports this idea. Because the level of lactate used in the study is the same as the level of lactate produced during high-intensity exercise in humans, these results are anticipated to occur in humans. 

In addition, lactate can inhibit ghrelin signaling in the hypothalamic ghrelin receptor (GHSR), which is a ghrelin receptor in the hypothalamus. Lactate inhibits hypothalamic ghrelin signaling by blocking the hypothalamic ghrelin receptor, GHS-R1α. Inhibition between ghrelin and its receptor inhibits ghrelin’s actions and decreases the synthesis of NPY/AgRP to suppress food intake (Figure 1). However, this mechanism is still not proven yet. This pathway was discovered by injecting lactate into embryonic kidney cells, with the result being a reduction in ghrelin signaling to GHSR-1α in the embryonic kidney cells. It is hoped that this action can also occur in the hypothalamus, as lactate is believed to be an antagonist of GHSR.

**D. THE ROLE OF PHYSICAL EXERCISE IN SUPPRESSING FOOD INTAKE THROUGH IL-6**

IL-6 was discovered to increase up to 100 times after bouts of aerobic exercise during a marathon. The rise in IL-6 induced by physical exercise was affected by the intensity and duration of physical exercise. Islam et al. discovered a rise in IL-6 during moderate-intensity continuous training (MICT), vigorous-intense continuous training (VICT), and sprint interval training (SIT). Among the three types of physical exercise, VICT led to the greatest increase in IL-6. This indicates that the IL-6 increase is proportional to the intensity of the physical exercise.

Control of IL-6 release mediated by physical exercise occurs at the stage of the IL-6 mRNA transcription process and is influenced by calcium (Ca²⁺). Continuous
muscle contraction will increase intracellular Ca\(^{2+}\) levels through the activation of phosphoinositide-3-kinase (PI3K), which will induce transcription factor activator protein 1 (AP-1). Skeletal muscle contraction also increases phosphorylation of c-Jun N-terminal kinase (JNK) through repeated membrane depolarization, which also activates AP-1. AP-1 activation will boost IL-6 transcription. IL-6 may inhibit food intake by modulating other appetite-regulating hormones in the periphery or by acting directly on the central regulation of food intake (Figure 2).\(^7\)\(^9\)

**THE PERIPHERAL ROLE OF IL-6 IN FOOD INTAKE SUPPRESSION**

Increasing the release of the anorexigenic hormone GLP-1 in the periphery is one mechanism by which IL-6 suppresses food intake.\(^6\) Exercise-induced IL-6 can enhance the production of proglucagon and prohormone convertase 1/3, resulting in the release of GLP-1 from pancreatic α cells and intestinal L cells (Figure 2).\(^\)\(^13\)\(^14\)\(^19\)

GLP-1 can reduce food intake by directly or indirectly altering activity in the central nervous system. However, the actual mechanism that plays a part in this is still unclear. After being secreted by pancreatic α cells and intestinal L cells, GLP-1 enters the blood vessels, reaches the portal circulation, enters the systemic circulation, and finally enters the brain’s area postrema (AP) by crossing the BBB.\(^14\)

GLP-1 binds to its receptor, GLP-1R, found in the AP of the central nervous system. Neurons in the nucleus of the solitary tract (NTS) that generate GLP-1 co-secrete GLP-1 in response to signals from the vagal nerves stimulated by GLP-1 in the periphery. The presence of GLP-1 released by NTS increases the amplification of peripheral GLP-1 signals. In addition, the signal from the NTS will be conveyed to other brain regions that express GLP-1R, such as ARC, the paraventricular nucleus (PVN), and the dorsomedial hypothalamus (DMH), where it will inhibit NPY/AgRP expression and enhance POMC expression. Nonetheless, this mechanism remains unknown.\(^14\)

**E. THE ROLE OF PHYSICAL EXERCISE IN SUPPRESSING FOOD INTAKE THROUGH IRISIN**

Physical exercise increases the requirement for intracellular Ca\(^{2+}\) to meet the needs of the...
skeletal muscles that must contract forcefully, therefore increasing the intracellular Ca\(^{2+}\) concentration. Increased intracellular Ca\(^{2+}\) concentrations cause an increase in the expression and activity of PGC-1\(\alpha\).\(^{16}\) PGC-1\(\alpha\) binds and/or activates transcription factors that express FNDC5, so an increase in PGC-1\(\alpha\) will result in an increase in FNDC5 levels. The more FNDC5 was produced, the more FNDC5 was folded, resulting in an increase in irisin production.\(^{15,16}\)

Irisin produced by skeletal muscle exerts a suppressive effect on food intake by inducing BDNF synthesis in the central nervous system.\(^{6}\) BDNF not only plays a role in neurogenesis, synaptogenesis, dendritic growth, and synaptic plasticity, but the results of a study conducted on experimental animals show that intracerebroventricular injection of BDNF also has an effect in the form of suppression of food intake and weight loss.\(^{20}\) So it can be concluded that BDNF can also have an anorexigenic effect in the central nervous system.\(^{6}\)

After being synthesized by skeletal muscle, irisin will enter the bloodstream, cross the BBB, and influence the activity and function of neurons in the central nervous system, including the neuron that produces BDNF.\(^{16}\) One mechanism that explains the effect of irisin on BDNF synthesis is through the PKA-cAMP-CREB signaling pathway. Irisin can stimulate the cyclic AMP (cAMP), protein kinase A (PKA), and cAMP response element-binding protein (CREB) signaling pathways in the cortex. This signaling pathway also regulates the expression of several genes that encode BNDF (Figure 3). It is unclear, however, whether irisin activates this signaling system directly or indirectly.\(^{15}\)

BDNF can reduce food intake by binding to its receptor, tyrosine kinase B (TrkB). The binding between BDNF and its receptor activates the PI3K/Akt pathway, which in turn activates the mammalian target of rapamycin complex 1 (mTORC1). Activating mTORC1 will stimulate protein synthesis and fat production, leading to an increase in muscle mass and a reduction in food intake.\(^{20}\)

**F. THE ROLE OF PHYSICAL EXERCISE IN SUPPRESSING FOOD INTAKE THROUGH LEPTIN**

Physical exercise can influence leptin levels, which in turn affect food intake. Acute bouts of exercise and resistance exercise are associated with a decrease in leptin levels following physical exercise. Long-term therapies consisting of aerobic activity, resistance exercise, and concurrent exercise are associated with decreased leptin levels. Physical exercise for two weeks increases leptin sensitivity and is believed to reduce leptin concentration in regular physical activity.\(^{7}\)

Physical exercise will affect proteins that act on insulin and leptin signaling at an early stage, such as the interaction between protein tyrosine phosphatase 1B (PTP1B) and insulin receptor (IR\(\beta\)), insulin receptor substrate 1 (IRS-1), and Janus kinase 2 (JAK2). Physical exercise will increase the phosphorylation of JAK2 and STAT3, which will affect the increasing signaling of leptin.
Phosphorylated STAT3 migrates to the nucleus and increases anorexigenic neuropeptide transcription. The activation of IRS 1/2 also increased following physical exercise. IRS 1/2 will also activate protein kinase B (Akt) and further phosphorylate forkhead box protein 01 (FOX01). Similar to STAT3, phosphorylated FOX01 migrates to the nucleus, inhibits the transcription of orexigenic neuropeptides, and suppresses food intake (Figure 4).

**FIGURE 4. EFFECT OF PHYSICAL EXERCISE ON LEPTIN AND ADIPOLECTIN SIGNALING PATHWAYS IN THE HYPOTHALAMIC ARC.**

**G. THE ROLE OF PHYSICAL EXERCISE IN SUPPRESSING FOOD INTAKE THROUGH ADIPOLECTIN**

Similar to leptin, adiponectin levels can be modified by physical exercise and are affected by the type, duration, and intensity of physical exercise, as well as by age and gender. Acute aerobic and resistance exercise raised adiponectin concentrations during or shortly after physical exercise.

Adiponectin has an excitatory effect on POMC neurons, which will cause depolarization and increase the effect of POMC neurons. In addition, adiponectin suppresses the activity of NPY and AgRP neurons directly, which has an effect on the activation of POMC neurons. Adiponectin causes POMC neurons to depolarize through binding to the AdipoR1 receptor, which stimulates the PI3K signaling pathway via the transient receptor potential canonical (TrpC) channel and is independent of the AMPK signaling pathway. Meanwhile, NPY and AgRP neuronal activity inhibition occurs through the activation of the PI3K signaling pathway mediated by the potassium (Katp) channel (Figure 4).

**III. CONCLUSION**

Physical exercise can suppress food intake by increasing the release of factors that play a role in regulating food intake. These variables, including lactate, IL-6, GLP-1, irisin, leptin, and adiponectin, might influence food intake by acting in the peripheral and/or by directly influencing the central regulation of food intake in the hypothalamus.

In the periphery, lactate inhibits ghrelin synthesis in gastric cells, resulting in a reduction in signals that activate NPY/AgRP neurons, while IL-6 works by increasing GLP-1 secretion, which has an anorexigenic effect in the hypothalamus. Meanwhile, lactate, IL-6, leptin, and adiponectin work directly in the central regulation of food intake by decreasing the production of NPY/AgRP and enhancing the secretion of POMC. Irisin acts directly in the central nervous system by influencing the secretion of BDNF, which also exerts an anorexigenic effect on the hypothalamus. Some of these mechanisms can show the role of physical exercise in suppressing food intake in an effort to overcome the problem of obesity.

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