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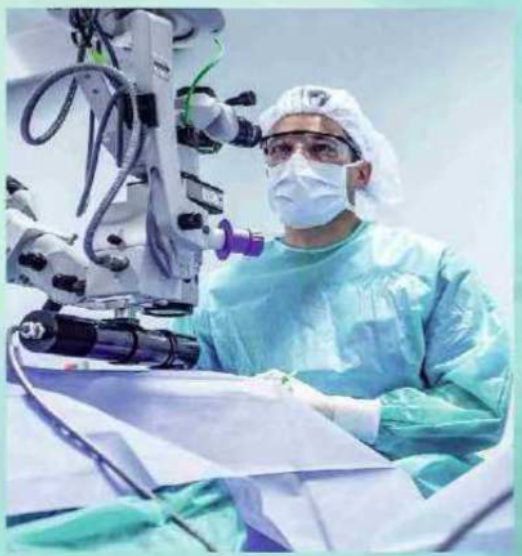

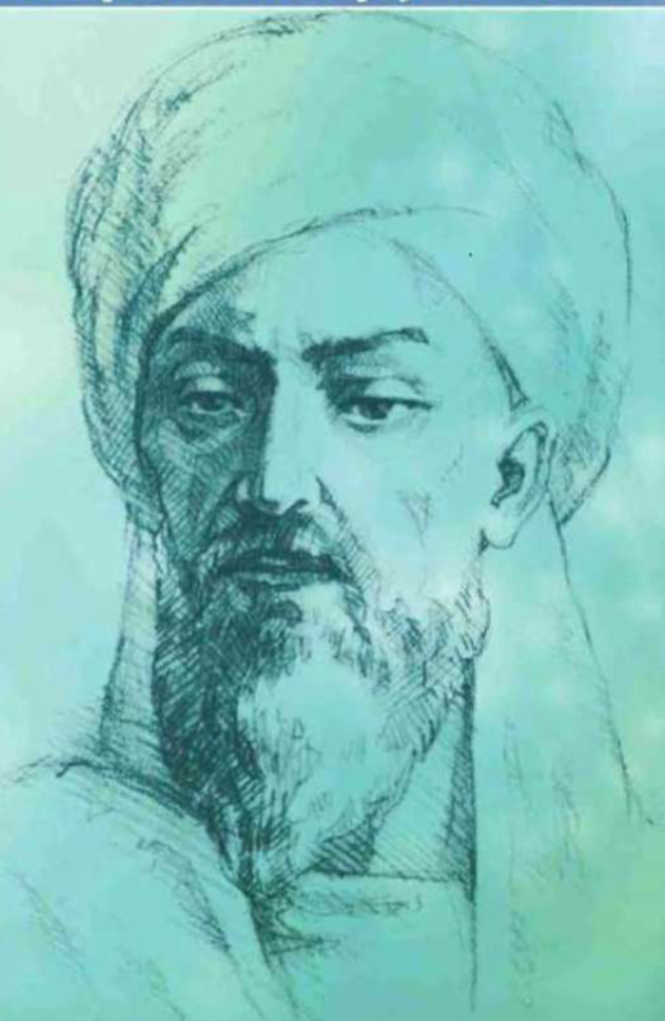

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НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

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www.bsmi.uz
https://newdaymedicine.com E: ndmuz@mail.ru
Тел: +99890 8061882

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NEUROHORMONAL REGULATION OF APPETITE AND SATIETY IN RELATION TO OBESITY PHYSIOLOGY

Islomova Mohinur Tolib kizi e-mail: Mohinur2519@gmail.com

Alfraganus University, Tashkent, Uzbekistan.
Tashkent city, Yunusabad district, Yukori Karakamish st 2a-house:
Email: info@alfraganusuniversity.uz +998781227557

✓ ***Resume***

The neurohormonal regulation of appetite and satiety is a complex process deeply intertwined with the physiology of obesity. Several hormones and neurotransmitters, primarily generated in the brain and gastrointestinal system, work in a coordinated manner to signal hunger or fullness, helping to maintain energy balance. Key players in this regulation include ghrelin, known as the "hunger hormone," which increases appetite and is typically elevated before meals. Conversely, leptin, produced by adipose (fat) cells, signals satiety to the brain, helping to reduce food intake once energy stores are sufficient.

In individuals with obesity, these regulatory systems can become dysregulated, leading to altered responses to hunger and fullness cues. Leptin resistance, a condition in which the brain becomes less responsive to leptin's signals, is commonly observed in obesity, reducing its effectiveness in curbing appetite. Similarly, insulin, another hormone that influences satiety, may become less effective in obesity, impacting glucose regulation and further complicating appetite control.

The hypothalamus, a brain region critical for regulating energy intake, plays a central role in interpreting and responding to these hormonal signals. Neurotransmitters such as dopamine and serotonin are also involved in the reward aspects of eating, often influencing food preferences and cravings, particularly for high-calorie foods. This reward pathway can override normal satiety signals, making it challenging to regulate food intake, especially in environments rich in highly palatable, calorie-dense foods. Understanding these mechanisms offers insights into potential therapeutic approaches for obesity, including treatments aimed at restoring hormonal balance and improving the body's response to hunger and satiety cues.

Keywords: the gastrointestinal tract, the hypothalamus, ghrelin, leptin, lipodystrophy, the Janus kinase.

НЕЙРОГОРМОНАЛЬНАЯ РЕГУЛЯЦИЯ АППЕТИТА И СЫТОСТИ В СВЯЗИ С ФИЗИОЛОГИЕЙ ОЖИРЕНИЯ

Исломова Мохинур Толибовна e-mail: Mohinur2519@gmail.com

Университет Альфраганус, Ташкент, Узбекистан.
Ташкент, Юнусабадский район, ул. Юкори Каракамыша, 2а-дом:
Email: info@alfraganusuniversity.uz +998781227557

✓ ***Резюме***

Нейрогормональная регуляция аппетита и сытости - сложный процесс, глубоко переплетающийся с физиологией ожирения. Несколько гормонов и нейротрансмиттеров, вырабатываемых в основном в головном мозге и желудочно-кишечном тракте, согласованно сигнализируют о голоде или сытости, помогая поддерживать энергетический баланс. Ключевыми игроками в этой регуляции являются грелин, известный как «гормон голода», который повышает аппетит и обычно увеличивается перед едой. И наоборот, лептин, вырабатываемый жировыми клетками, сигнализирует мозгу о сытости, помогая снизить потребление пищи, как только запасов энергии становится достаточно.

У людей с ожирением эти регуляторные системы могут быть нарушены, что приводит к изменению реакции на сигналы голода и сытости. Лептинорезистентность - состояние, при котором мозг становится менее чувствительным к сигналам лептина, - часто наблюдается при ожирении, что снижает его эффективность в сдерживании аппетита. Аналогичным

образом, инсулин, другой гормон, влияющий на сытость, может стать менее эффективным при ожирении, что влияет на регуляцию уровня глюкозы и еще больше усложняет контроль аппетита.

Гипоталамус, область мозга, критически важная для регулирования потребления энергии, играет центральную роль в интерпретации и реагировании на эти гормональные сигналы. Нейротрансмиттеры, такие как дофамин и серотонин, также участвуют в вознаграждении за прием пищи, часто влияя на предпочтения и тягу к еде, особенно к высококалорийным продуктам. Этот путь вознаграждения может перекрывать нормальные сигналы сытости, что затрудняет регулирование потребления пищи, особенно в условиях изобилия очень вкусных и калорийных продуктов. Понимание этих механизмов дает представление о потенциальных терапевтических подходах к лечению ожирения, включая методы, направленные на восстановление гормонального баланса и улучшение реакции организма на сигналы голода и сытости.

Ключевые слова: желудочно-кишечный тракт, гипоталамус, грелин, лептин, липодистрофия, киназа Януса.

Introduction

The processes of appetite and satiety involve intricate hormonal interactions, primarily between the gastrointestinal tract and the hypothalamus, which then provide feedback to regulate these sensations. Within the hypothalamus, specific regions respond to hormonal signals to create the sensations of hunger or fullness, prompting food intake or the feeling of satiety. The hormones ghrelin and leptin play a central role in this regulation: ghrelin, known as the "hunger hormone," was initially identified through its receptor, the growth hormone secretagogue receptor, before its role in promoting hunger was fully understood [1].

Leptin, discovered mainly as a hormone involved in body weight regulation, also plays a significant role in appetite and satiety. Research has shown that ghrelin levels increase before meals and decrease afterward, while leptin levels adjust accordingly to influence feelings of fullness [2]. Together, signals from ghrelin and leptin impact different nuclei in the hypothalamus, regulating hunger and satiety cues to support energy balance. Any imbalance or disruption in these hormonal pathways can significantly impair the body's ability to maintain energy homeostasis [3].

Issues of concern

Understanding the roles of ghrelin and leptin has significantly advanced therapeutic strategies for various health conditions. As obesity rates have surged over the past 50 years, researchers have sought effective ways to address this growing public health issue, which is associated with numerous secondary diseases [4]. Research on leptin applications continues to progress, aiming to treat obesity and conditions like lipodystrophy [5]. Similarly, studies on ghrelin have focused on its potential benefits for individuals with eating disorders and growth deficiencies [6].

Knowledge of how these hormones interact with specific hypothalamic nuclei has been key in developing treatment options for several disorders. Imbalances or reduced sensitivity to ghrelin and leptin can contribute to issues such as anorexia or overeating, with distinct pathophysiological consequences that may emerge due to hormonal imbalances. Thus, maintaining appropriate levels of ghrelin and leptin is essential for preserving energy homeostasis. Given the global rise in obesity and its links to secondary diseases, therapeutic approaches, such as managing leptin levels, are being actively investigated [7].

Cellular Level

Since the discovery of ghrelin and leptin, researchers have examined their roles in detail. Initially recognized for ghrelin's association with growth hormone and leptin's effect on body weight regulation, numerous studies have since explored their broader functions. Findings reveal that these hormones mainly act within specific nuclei of the hypothalamus to modulate appetite and satiety.

Ghrelin is a 28-amino acid peptide encoded by the GHRL gene on chromosome 3 [8]. Its production occurs primarily in X/A-like cells, which store ghrelin in dense granules. Ghrelin's mRNA is predominantly present in gastric tissue, where it helps regulate energy balance in coordination with the hypothalamus. Ghrelin undergoes a series of post-transcriptional modifications, transforming from preproghrelin to proghrelin, and ultimately to its active forms: non-acylated ghrelin (found abundantly in the bloodstream) and acylated ghrelin [9]. The hormone's primary receptor is the growth hormone secretagogue receptor type 1a (GHS-R1a), a G-protein-coupled receptor located in areas such as the hypothalamus, where it plays a vital role in energy homeostasis regulation [10].

Leptin, produced by the obese gene on chromosome 7, is mainly synthesized in adipose tissue as a 167-amino acid peptide conserved across species [11]. It circulates in the blood in response to body fat storage, sending signals to the brain to regulate energy balance. Leptin's main receptor, LepR, exists in various subtypes distributed throughout the hypothalamus. Leptin can cross the blood-brain barrier, interacting with hypothalamic regions like the arcuate nucleus, ventromedial nucleus, and lateral hypothalamus, where it promotes satiety and inhibits hunger, thereby influencing energy homeostasis. Additionally, the leptin receptor subtype LepRb initiates signaling cascades, including the Janus kinase 2/extracellular signal-regulated kinases pathways, which further regulate these responses [12]. Higher body mass index and body fat percentage correlate with increased leptin levels in blood plasma. Beyond fat storage, leptin release varies with factors such as food intake, gender, age, physical activity, and blood glucose levels [7].

Development

Achieving homeostasis in appetite and satiety control through hormones like ghrelin and leptin depends on the hypothalamus's ability to integrate various hormonal signals. The hypothalamus is divided into three main zones: periventricular, medial, and lateral. Most of its nuclei, critical for hormonal regulation, reside in the medial region, which includes subdivisions such as the preoptic area, the anterior (supraoptic) region, the middle (tuberal) region, and the posterior (mamillary) region [13]. Within this framework, the lateral hypothalamus, arcuate nucleus, and ventromedial hypothalamus, located in the middle (tuberal) region, are central to managing sensations of hunger and fullness [14].

The hypothalamus's development is essential for sustaining this balance. Morphogens like Wnt8 facilitate anterior-posterior patterning within the neural plate, leading to hypothalamus formation [15]. In particular, the inhibition of Wnt signaling is necessary for the anterior organization of the neural plate, which eventually differentiates into the hypothalamus. Specific regulators contribute to the development of individual hypothalamic regions, each responsible for distinct physiological roles. For instance, the ventromedial hypothalamus originates from Rax and Nkx2.1 expressions, whereas Foxb1 expression in progenitor cells plays a role in the formation of the lateral hypothalamus, though its exact cell fate determinants remain unclear [15]. As research advances, understanding of the regulatory elements and developmental stages of the hypothalamus continues to grow, with many mechanisms still under investigation.

Organ Systems Involved

Appetite and satiety regulation relies on signals from the gut and adipose tissue. The gut primarily produces ghrelin, which triggers hunger, while leptin, originating in adipose tissue, promotes satiety. These signals are processed in the hypothalamus, which serves as the body's central regulator for energy balance. Circulating ghrelin acts on the lateral hypothalamus, while leptin targets the arcuate nucleus in the middle (tuberal) region, helping the body adjust to its energy needs. The lateral hypothalamus is also involved in forming and storing food-related memories, which aids in predicting food availability in a given environment through ghrelin interactions [16].

In addition to ghrelin and leptin, other short-acting signals from the gut, like cholecystokinin (CCK) and gut distension, promote feelings of fullness and satiety [17]. CCK activates the nucleus of the solitary tract, which then relays this information to the hypothalamus. Meanwhile, longer-acting signals such as peptide YY and glucagon-like peptide inhibit appetite, maintaining energy homeostasis over the long term. These mechanisms emphasize the hypothalamus's role as the key integrator of various hunger and satiety cues. Each signal acts on different hypothalamic nuclei to modulate energy balance, and any disruption to these signaling pathways can negatively impact an organism's overall energy equilibrium. The gut and adipose tissue are thus vital in signaling when the body requires more or less energy intake.

Function

The primary function of various hormones involved in appetite and satiety regulation is to support energy homeostasis. Hormones like ghrelin, leptin, cholecystokinin, and other peptides send peripheral signals to the hypothalamus, where these signals are integrated to control hunger and fullness. Imbalances in these hormones can lead to pathologies, some of which will be discussed later in this article. In particular, ghrelin and leptin are the two hormones most closely associated with the regulation of energy balance, as they influence sensations of hunger and satiety. Any shift in the balance between ghrelin and leptin significantly impacts the body's ability to meet energy demands and regulate storage, leading to potential pathophysiological issues.

Ghrelin: Initially identified as a growth hormone-releasing peptide that acts on the hypothalamus, ghrelin levels were later found to increase before meals, thus promoting appetite and earning the name "hunger hormone." [3]. It acts primarily on the lateral hypothalamus, the brain region responsible for hunger sensations. While ghrelin is known mainly for stimulating appetite, it also plays roles in regulating sleep-wake cycles, taste perception, and glucose metabolism [19]. Studies have shown that ghrelin can influence glucose metabolism by decreasing insulin release, which highlights its complex interaction with energy regulation [20].

Leptin: Often considered the counterbalance to ghrelin, leptin serves as the body's primary satiety signal. Together, ghrelin and leptin work in harmony to regulate energy homeostasis. The ventromedial region of the hypothalamus, responsible for satiety, responds to leptin, while leptin simultaneously inhibits the lateral hypothalamus to counteract the effects of ghrelin. As an adipocyte-derived hormone, leptin communicates with the medial hypothalamus about the body's energy storage status. Beyond appetite control, leptin is involved in regulating reproduction, blood pressure, and immune responses, all of which can influence overall energy metabolism [21]. The link between inactive leptin signaling and obesity has been the subject of extensive research, illustrating leptin's critical role in energy balance and metabolic health [22].

Mechanism

Activation of specific receptors within these pathways is essential for achieving the regulatory balance between hunger and fullness. Communication between the gastrointestinal (GI) tract and the hypothalamus relies on hormones targeting appropriate receptors within the central nervous system (CNS). Ghrelin, produced in the GI tract, targets hypothalamic regions to signal hunger. The sympathetic and parasympathetic nervous systems play crucial roles in informing the brain about when to initiate eating. Ghrelin binds to the growth hormone secretagogue receptor, GHSR-1a, to stimulate sensations of hunger and anticipation of food [10]. Studies suggest that the body can adapt to ghrelin signaling based on metabolic status and environmental cues, fine-tuning the hunger response over time [23].

While the complete mechanism of leptin's regulation of energy homeostasis and blood glucose is still under investigation, it is known that leptin receptor (LepRb) expression is higher in the CNS. Evidence indicates that leptin's action within the CNS can effectively lower blood glucose levels [24]. Leptin receptors primarily have a GABAergic effect in various hypothalamic nuclei, such as the ventromedial nucleus, dorsomedial nucleus, lateral hypothalamus, and arcuate nucleus, with its primary regulatory effect occurring within the arcuate nucleus. The arcuate nucleus contains two primary neuron types: pro-opiomelanocortin (POMC) and agouti-related protein (AgRP) neurons [24].

Leptin stimulates POMC neurons and inhibits AgRP neurons, projecting to the ventromedial hypothalamus. Activated POMC neurons release alpha-melanocyte-stimulating hormone (alpha-MSH), which acts to suppress food intake. Research has also identified leptin receptors in the hippocampus, where leptin influences cognitive function and neural plasticity [25]. Leptin's role has been investigated across individuals with varying body compositions, revealing distinct mechanisms and potential involvement in tumor formation and metastasis [26].

Pathophysiology

Maintaining a balance between ghrelin and leptin is essential for regulating energy homeostasis. The interaction of signals from the GI tract and adipose tissue enables appropriate communication with hypothalamic nuclei to manage hunger and satiety. Imbalances in these hormone levels can lead to pathophysiological issues related to energy and weight regulation.

Obesity: The global rise in obesity has brought a surge in associated diseases, such as diabetes, hypertension, liver disease, stroke, and myocardial infarction. Additionally, obesity is often linked to social stigma and disadvantages, including challenges with employment [4]. Leptin resistance, a condition common in obesity, occurs when high levels of leptin no longer reduce appetite effectively, likely due to impaired leptin signaling pathways [27]. While healthy responses to elevated leptin levels usually decrease food intake and promote weight loss, mutations in the leptin gene or signaling pathway can disrupt this balance, contributing to obesity. Resistance may stem from leptin's limited ability to reach the hypothalamus or downstream signaling defects [5].

Eating Disorders: Conditions like anorexia nervosa and bulimia nervosa, historically viewed as psychiatric disorders, have also shown a hormonal component. Individuals with anorexia often exhibit elevated ghrelin levels, and those with bulimia have similarly high fasting ghrelin levels, indicating a

possible physiological basis for these conditions [28]. This highlights the role of ghrelin and appetite-related hormones in disorders that were once primarily associated with mental health.

Prader-Willi Syndrome (PWS): This genetic disorder, linked to chromosome 15q11.2-q13, is marked by hyperphagia and symptoms including hypotonia, developmental disabilities, and distinctive physical features. Some PWS patients show elevated ghrelin levels during fasting and fed states, though the relationship between ghrelin and PWS remains complex, as not all individuals with PWS have raised ghrelin levels, and early hyperphagia may occur without changes in ghrelin levels [29][30][31].

Rheumatoid Arthritis: Beyond weight regulation, leptin also has pro-inflammatory effects, especially within joint tissues. Studies have shown that leptin levels are elevated in patients with rheumatoid arthritis, suggesting a link between energy metabolism and inflammatory processes [32].

Mood Disorders: Ghrelin and leptin influence not only hunger but also reward and motivation pathways, which connect to mood regulation, stress, anxiety, and depression. While some studies suggest leptin may reduce depressive symptoms, others find no significant difference in ghrelin levels between those with depression and healthy individuals, leaving the exact role of these hormones in mood disorders under investigation [33][34].

Together, these findings underscore the complex role of ghrelin and leptin in both physical and mental health, illustrating how disturbances in their regulation can lead to diverse pathophysiological outcomes.

Clinical Significance

Ghrelin and leptin are key hormones with regulatory effects that hold clinical promise in treating various disorders. Ghrelin, in particular, has shown potential as a therapeutic agent in cancer cachexia due to its anti-inflammatory properties, as well as its effects on muscle catabolism, anti-apoptotic mechanisms, and ability to reduce the adverse impacts of chemotherapy [35]. Beyond this, ghrelin's broader influence on body metabolism includes roles in anti-inflammation, cardiac performance improvement, and stress regulation, with ongoing research exploring these avenues for therapeutic use [36]. Synthetic ghrelin-receptor agonists, such as Anamorelin, have demonstrated beneficial outcomes in managing cachexia symptoms, further supporting ghrelin's therapeutic potential [37].

Leptin's role in weight regulation has also been a focus in clinical trials exploring its impact on weight loss interventions. By understanding leptin's effects on energy balance and metabolism, researchers hope to develop leptin-based treatments for obesity and other metabolic disorders [38]. Many of these studies are in advanced stages, with the potential to provide clinically significant benefits in the near future.

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