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Review

Exploring hormonal dynamics in obesity: Leptin, ghrelin, and nesfatin-1

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ABSTRACT

Obesity is a disease that develops as a result of multifactorial causes such as genetic, environmental, biological, psychosocial, and economic factors, leading to excessive fat accumulation and a body mass index exceeding 30 kg/m^2. In our bodies, there are appetite-stimulating and suppressing hormones that regulate nutrient intake and control energy metabolism, either directly secreted or via the hypothalamus. This review examines the relationships between obesity and major appetite-suppressing hormones, including the protein-based leptin hormone synthesized from adipose tissue and nesfatin-1, a neurohormone expressed from adipose tissue, pancreas, and brain, as well as ghrelin, a peptide hormone also known as an appetite stimulant.

Keywords: Ghrelin, hormones, leptin, nesfatin-1, obesity.

Obesity is a multifactorial disease characterized by an excess accumulation of fat in the body. According to body mass index (BMI): 25.0-29.9 kg/m^2 is classified as overweight, 30 kg/m^2 as obesity, and those exceeding 30 kg/m^2 are termed morbidly obese and super morbidly obese. The number of obese individuals is increasing day by day in many developed countries.[1]

Although the exact cause of obesity is unknown, biological, psychosocial, behavioral, genetic factors, socioeconomic status, and cultural influences appear to be associated with obesity.[2] In obesity, excessive intake of calorie-rich foods increases body weight, and excess energy is stored as fat, leading to adiposity. One of the contributing factors to obesity is an increase in fat tissue due to decreased physical activity. Psychological factors can also contribute to obesity. For example, situations such as the death of a close relative, severe illness, exposure to stress, or experiencing psychological distress may encourage individuals to view eating as a means of escaping emotional tension. When children are pressured by their parents to overeat during childhood, the number of newly formed fat cells increases, leading to increased fat storage. The fat cells of obese children are three times more numerous than those of children with normal weight. Neurogenic disorders are among the factors contributing to obesity. In studies, it has been observed that lesions occurring in the ventromedial nuclei of the hypothalamus lead to obesity in animals due to overeating. In individuals with pituitary tumors extending towards the hypothalamus, obesity can develop by damaging the hypothalamus. Another factor contributing to obesity is genetic factors. Obesity genes can result from the disruption of pathways regulating feeding centers, fat storage, and energy consumption. There are three reasons why obesity may be monogenic: mutations in the melanocortin receptor 4 (MCR-4), congenital absence of the leptin gene, and mutations in the leptin receptor, which trigger obesity through the combination of

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environmental factors.[3] According to scientific research, genetic diseases such as Bardet-Biedl syndrome and Prader-Willi syndrome can contribute to obesity.[4]

THE ROLE OF THE HYPOTHALAMUS IN FOOD INTAKE

The hypothalamus, a central region in the brain, plays a key role in regulating feeding behavior and controlling food intake (including enjoyment of food, food quality, and taste) through signals received from peripheral organs. It also regulates energy metabolism. By integrating central information to regulate energy balance, it maintains body homeostasis. Within the hypothalamus, the arcuate nucleus (ARC), ventromedial, dorsomedial, periventricular, and lateral hypothalamic areas play important roles in regulating energy metabolism.[5]

The neurons in the ventromedial and lateral regions serve to control food intake by acting as sensitive glucose receptors to the arteriovenous glucose difference. Neurons in the ventromedial region are stimulated by food intake, leading to the creation of a feeling of satiety through alpha (α)-adrenergic receptors, thereby halting food intake. Lesions occurring in the ventromedial area result in excessive food cravings and a lack of satiety, leading to obesity. Neurons in the lateral region induce hunger through the stimulation of beta-adrenergic and dopaminergic receptors. Ventral and lateral neurons mutually inhibit each other's food intake, thus regulating control. Through these reciprocal relationships, they maintain balance.[6]

The ARC located in the hypothalamus contains two distinct types of neurons that control appetite and energy expenditure: proopiomelanocortin (POMC) neurons, which produce alpha-melanocyte stimulating hormone (α-MSH) along with cocaine- and amphetamine-regulated transcript, and neurons produce appetite-stimulating substances, such as neuropeptide Y (NPY) and agouti-related peptide (AgRP). The α-MSH secreted by POMC neurons reduces food intake and increases energy expenditure by stimulating melanocortin receptors (MCRs) found in neurons of the paraventricular nucleus. At least five types of MCRs exist. Melanocortin receptor 3 and MCR-4 play a particularly important role in regulating food intake and energy balance. Activation of MCR-3 and MCR-4 reduces food intake and energy expenditure. Activation of AgRP neurons suppresses MCR-3 and MCR-4, leading to increased food intake and energy expenditure. When energy stores in the body are depleted, appetite-stimulating NPY is activated, inhibiting MCR-4 and increasing appetite to enhance food intake.[7]

There are many peptide and protein hormones that affect or directly act on food intake through the hypothalamus. These hormones are classified into two groups based on their duration of action, short-term or long-term. Short-term regulation is concerned with preventing overeating during meals. Short-term regulators include ghrelin (appetite stimulant), nesfatin-1 (appetite suppressant), and cholecystokinin (appetite and energy intake suppressant). Long-term regulation, on the other hand, aims to maintain normal levels of body energy stores for an extended period. Long-term regulators include NPY and AgRP as appetite stimulants, and insulin, leptin, obestatin, POMC, and MCR-4 as appetite suppressants.[8]

LEPTIN

Leptin was first discovered by Zhang *et al.*[9] in 1994, a 167-amino acid protein hormone named after the Greek word 'leptos' (thin). It is located on the long arm of chromosome 7 (7q31) in humans and is primarily produced in adipose tissue by the ob gene (human obese gene), encoded into messenger ribonucleic acid (mRNA). Hence, another name for the leptin hormone is Ob protein.

Leptin plays an important role in regulating body weight homeostasis. Levels of leptin are proportional to body fat mass. Leptin secretion is regulated by circadian rhythm, with leptin secretion being highest from midnight to the early hours of the morning. Leptin secretion is at its lowest levels in the afternoon.[10,11] The nerves and neurohormonal components in the brain regulate leptin secretion in accordance with circadian rhythm, and it is synthesized primarily in adipose tissue but also in various tissues

throughout the body. Leptin is also secreted by the stomach, placenta, mammary glands, ovarian follicles, heart, bone/cartilage tissue, some fetal organs, and the brain.[12]

Mechanisms of leptin action

In the hypothalamus, ventromedial, paraventricular nuclei, arcuate nuclei, amygdaloid nuclei, and choroid plexus contain five different receptors for leptin: ObRa, ObRb, ObRc, ObRe, and ObRf forms. Protein-based molecules such as Janus kinase 2 (JAK-2), and signal transducers and activators of transcription (STAT) play roles in leptin receptor signaling. The most important and longest form, ObRb, directly participates in initiating signaling with its intracellular extension. ObRa and ObRc forms allow leptin to cross the blood-brain barrier (BBB).[13]

As mentioned earlier, the ARC in the hypothalamus contains the appetite-stimulating NPY. Neuropeptide Y becomes active when energy stores are depleted, inhibiting MCR-4 and increasing food intake. Leptin binds to the ObRa receptor in the hypothalamus, leading to phosphorylation of the receptor's intracellular extension by JAK-2. The phosphorylated intracellular domain then associates with the STAT protein, detaches from the cell membrane, and enters the cell.[14] It reduces the amount of NPY mRNA and inhibits its secretion. Simultaneously, it stimulates the production of α-MSH, reducing food intake.[15]

Leptin deficiency and resistance

Leptin deficiency can be congenital or acquired. Congenital leptin deficiency results from leptin mutations leading to obesity and dysregulation of hypothalamic pathways, which can be corrected with leptin hormone replacement therapy.[16,17] Acquired leptin deficiency, on the other hand, is associated with hypothalamic-pituitary-gonadal axis dysfunction due to prolonged decreases in exercise, stress, or food intake, especially in cases of low body weight, resulting in menstrual irregularities.[16,18]

Leptin resistance can occur due to impairment in leptin's passage through the BBB or dysfunction of leptin receptors.[19] The leptin hormone exerts its effects by crossing the BBB through carriers. Dysfunction in these carrier functions can lead to leptin resistance.[20]

The relationship between obesity and leptin

The levels of leptin hormone, which has the effect of increasing energy expenditure and reducing appetite, convey information about the accumulated energy in fat tissue to the hypothalamus. Accordingly, an increase in leptin levels leads to decreased appetite and increased energy expenditure, while conversely, when leptin levels are low, appetite increases while energy expenditure decreases.[21] When serum leptin levels of obese individuals are examined, they are found to be higher compared to normal individuals.[22] Due to leptin resistance in hypothalamic receptors in obese individuals, high levels of leptin fail to control body weight effectively.[23,24] In obese individuals, differences in serum leptin levels between genders are observed. Female obese individuals tend to have higher leptin levels compared to male obese individuals, and a positive correlation has been identified between BMI and serum leptin levels.[25]

Obesity in humans does not solely arise from leptin deficiency; obese individuals also exhibit resistance to leptin. When examining the reasons for leptin resistance, it can stem from dysfunction in carriers at the BBB or at the level of receptors in the central nervous system.[20] According to the findings of the study, the primary cause of obesity stems from abnormalities in the transport of leptin across the BBB.[26]

GHRELIN

In 1976, Banks[27] found that opioid peptide derivatives did not exhibit opioid activity but rather showed a weak growth hormone-releasing effect. Therefore, they termed them as growth hormone secretagogues (GHS). Attempts were made to isolate the endogenous GHS receptor ligand from regions where growth hormone-releasing substance receptor synthesis occurs, such as the brain, pituitary, and hypothalamus, but these efforts were unsuccessful.[28-30] In 1999, Kojima et al.[31] isolated the endogenous ligand of the growth hormone secretagogue receptor (GHS-R) from the stomach and named it ghrelin, combining the root of the word 'grow,' which signifies development, with 'relin,' which denotes secretion. Ghrelin exists in two forms in the body,

acylated and desacylated, with a half-life of 15-20 minutes. An eight-carbon fatty acid is attached to the third amino acid, serine, at the N-terminal end of ghrelin. This attached fatty acid is called an octanoyl group and forms the acylated part, or the active part, of ghrelin. Desacyl ghrelin, which constitutes the majority of circulating ghrelin, lacks the octanoyl group. Ghrelin is the only hormone activated by a fatty acid molecule. When bound to a fatty acid molecule, ghrelin becomes hydrophobic, allowing it to easily pass through the BBB and reach the hypothalamus and pituitary. The precursor molecule of ghrelin, proghrelin, consists of 117 amino acids.[32,33]

Ghrelin is primarily produced by X/A-like cells located in the oxyntic glands of the submucosal layer of the stomach.[34] Ghrelin is released from tissues such as the hypothalamus, pituitary gland, salivary gland, thyroid gland, small intestine, kidney, heart, pancreas, lungs, placenta, gonads, immune system, and breast.[35-38]

The ghrelin hormone is involved in the synthesis of growth hormone and plays a role in increasing appetite and regulating satiety by affecting fat tissue and serum levels of cortisol, catecholamines, adrenocorticotropic hormone (ACTH), prolactin, and aldosterone. Ghrelin hormone functions in the opposite way to leptin hormone, increasing appetite, raising food intake, and disrupting energy balance, leading to excessive weight gain.[39] In humans, plasma ghrelin levels increase with feelings of hunger and decrease with feelings of satiety.[40]

The mechanism of action of ghrelin

The GHS-R is a G protein-coupled receptor with seven transmembrane regions.[41] The mRNA of GHS-R is synthesized in the arcuate and ventromedial nuclei as well as in the hippocampus.[42] The mRNA of GHS-R is found in various tissues and organs including hypothalamic nuclei, pituitary gland, heart, lungs, liver, kidneys, pancreas, stomach, small and large intestines, adipose tissue, and immune cells.[36]

The growth hormone secretagogue receptor is encoded by two different mRNAs. The GHS-R1a is involved in the regulation of appetite and energy balance in the central nervous system, and it is found in hypothalamic nuclei, the dorsal vagal complex, and the mesolimbic dopaminergic system.[43] The GHS-R1b is not active because it lacks certain specific transmembrane domains.[44]

As we mentioned, for ghrelin to be active, it needs to be in its functional form called acylated ghrelin, which occurs when the eight-carbon fatty acid binds to the third amino acid, serine. The enzyme responsible for facilitating the binding of this fatty acid is ghrelin O-acyltransferase, which plays a role in the activation of ghrelin.[33,45]

The relationship between obesity and ghrelin

Ghrelin exerts its effects on appetite through three pathways. Firstly, the ghrelin hormone synthesized in the stomach reaches the ARC through active transport via the bloodstream, thereby stimulating the appetite center. Secondly, the ghrelin hormone synthesized peripherally stimulates vagal afferent nerve terminals and activates the hypothalamus by inducing GHS-R expression. Thirdly, the ghrelin hormone synthesized in the hypothalamus increases the production of NPY and AgRP in the ARC while suppressing POMC production. The ghrelin hormone stimulates appetite by increasing its serum levels in response to the depletion of energy stores.[46,47] The levels of ghrelin in lean individuals are higher compared to obese individuals, and an increase in ghrelin levels has been observed in obese individuals following weight loss due to diet and exercise.[48] When comparing plasma ghrelin levels between individuals with anorexia nervosa and obese individuals, individuals with anorexia nervosa tend to have higher plasma leptin levels compared to obese individuals.[49]

NESFATIN-1

Discovered by Oh-I et al.[50] in 2006, nesfatin-1 is an anorexigenic (appetite-reducing) neurohormone derived from nucleobindin 2 (NUCB2) protein expressed in the hypothalamus, adipose tissue, pancreas, gastric mucosa, and the brain. The NUCB2 consists of 396 amino acids, with the N-terminal nesfatin-1 spanning amino acids 1-82, nesfatin-2 spanning amino acids 85-163, and nesfatin-3 spanning amino acids 166-396. The first 23 amino acids of nesfatin-1, which comprise 82 amino acids in total, exhibit activity in inhibiting food intake. However, definitive data regarding the activity of nesfatin-2 and nesfatin-3 are yet to be obtained.[51,52]

The mechanism of action of nesfatin-1

The nesfatin-1 hormone activates neurons containing POMC, which is a precursor to ACTH, in the ARC of the hypothalamus or in the nucleus tractus solitarius in the brainstem. It crosses the BBB through neural network interactions to reach central brain centers, both endogenously and exogenously regulated.[51,53] The expression of nesfatin-1 is associated with the satiety hormone α-MSH. Alpha-melanocyte stimulating hormone increases the expression of the NUCB2 gene and nesfatin-1 expression in the paraventricular nucleus.[54] The NUCB2/nesfatin-1 in the brain suppresses food intake by exerting its secretory effects through receptors such as oxytocin, POMC/MSH, corticotropin-releasing factor, histamine, serotonin, and thyrotropin-releasing hormone.[51]

The relationship between obesity and nesfatin-1

Studies investigating the relationship between plasma nesfatin-1 levels and obesity are contradictory. Nesfatin-1 levels are inversely related to total body fat levels.[55] In obese individuals, as nesfatin-1 levels increase, the percentage of body fat decreases. It has been observed that obese individuals with low nesfatin-1 levels have an increase in carbohydrate, protein, and energy intake.[56] In obese children, serum nesfatin-1 levels are lower compared to normal-weight children.[57]

Contrary to these results, in a study, serum nesfatin-1 levels in obese individuals were higher compared to normal-weight individuals.[58] Supporting this, another study found a positive correlation between nesfatin-1 and BMI.[54,55,59]

Congenital nesfatin-1 deficiency has been associated with early-onset obesity, characterized by the deficiency of prohormone convertase 1, which converts NUCB2 into nesfatin-1, 2, and 3.[60] The research identified the first genetic variation of nesfatin-1 in obese individuals, revealing seven different sections of the NUCB2 gene. These variations did not affect circulating levels, but it is speculated that these diverse variations may trigger obesity in the brain through nesfatin-1. Further scientific studies are needed to investigate this possibility.[61] Further studies are expected to investigate the roles of gender differences, age, body weight, and different assessment methods.[54] Long-term studies providing conclusive evidence on the effect of nesfatin-1, known to cross the BBB and reduce food intake, in obese individuals are needed.[63,63]

In conclusion, obesity is a multifactorial condition characterized by an excess accumulation of body fat, where energy intake exceeds energy expenditure, and the BMI exceeds 30 kg/m^2. Factors contributing to obesity can be attributed to genetic, environmental, psychosocial, and economic factors. Reduced physical activity, overeating, particularly during childhood leading to excessive fat accumulation, and lesions in the ventromedial nuclei of the hypothalamus triggering overeating desires can lead to obesity. Another contributing factor is genetics, where mutations in MCR-4, deficiency of the leptin gene, or mutations in the leptin receptor, combined with environmental factors, can trigger obesity. There are many factors contributing to obesity. The hypothalamus is a region in the brain that plays a role in controlling food intake and regulating energy metabolism There are hormones that affect or directly affect nutrient intake through the hypothalamus, including appetite-stimulating and appetite-suppressing hormones. Appetite-suppressing hormones such as leptin and nesfatin-1, as well as appetite-stimulating hormones such as ghrelin, are associated with obesity. The leptin hormone restricts food intake and regulates energy metabolism by providing negative feedback to the hypothalamus. In obese individuals, higher levels of leptin are found compared to normal individuals. However, leptin resistance may occur due to abnormalities in carriers at the blood-brain barrier or disruptions in receptors. Ghrelin hormone, unlike leptin hormone, is an appetite-stimulating hormone and is known as a growth hormone-releasing peptide Ghrelin hormone stimulates appetite in three different ways: Firstly, ghrelin hormone synthesized in the stomach stimulates appetite by actively circulating through the bloodstream. Secondly, the ghrelin hormone synthesized peripherally stimulates the hypothalamus by increasing the expression of ghrelin hormone receptors.

Thirdly, the ghrelin hormone synthesized in the hypothalamus suppresses POMC production. However, studies on the relationship between appetite-suppressing hormones such as nesfatin-1 and obesity are contradictory. Therefore, more scientific research is needed to better understand the relationship between hormones and obesity.

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