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Review

Ghrelin: A Link Between Food Reward and Motivation

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ABSTRACT

Ghrelin is a peptide hormone generated in the stomach by the ghrelin O-acyltransferase enzyme, which has an orexigenic effect in the central nervous system when it binds to peripheral receptors. Ghrelin secretion increases before meals, increasing food intake by signaling hunger in the hypothalamus via homeostatic mechanisms. Ghrelin interacts with various regions of the brain to adjust food intake and boost food reward at the same time. In addition to its effects on feeding behavior, the hormone ghrelin, which interacts with the hypothalamic-pituitary-adrenal axis, has an impact on stress and various psychiatric disorders produced by stress. The effects of the ghrelin hormone on nutritional behavior, reward, motivation, and stress were described in this review with scientific examples.

Keywords: Ghrelin hormone, ghrelin O-acyltransferase (GOAT), hypothalamic-pituitary-adrenal axis, nutritional behavior, reward, motivation

Ghrelin is a gastric peptide hormone that controls food intake, body weight, taste sensitivity, reward, cognition, learning, and memory.[1,2] Ghrelin activities are primarily mediated through the activation of the growth hormone secretagogue receptor type-1a (GHS-R1a); however, ghrelin can also act on other receptors in some tissues.[3] The GHS-R1a is expressed specifically in the pituitary gland and central nervous system where ghrelin signals regulate various functions.[4,5]

Ghrelin is the only known orexigenic hormone. It is known to increase food intake when administered to humans and animals.[6] Furthermore, ghrelin promotes food intake in humans and rodents through the rewarding modulation of certain foods and the motivation to get them. Several regions of the brain are affected by ghrelin's actions, including the mesolimbic pathways, which govern hedonic feeding and reward processing.[7] In addition, it is known that ghrelin has functions of activating neuroendocrine systems and the hypothalamic-pituitary-adrenal (HPA) axis with its effect on increasing plasma levels of adrenocorticotropic hormone (ACTH) and cortisol.[8,9] Considering these functions, various studies have been conducted on the relationship between ghrelin release and stress management. It has been observed that ghrelin secretion increases during periods of hunger and stress and are rapidly mixed into the blood; however, it was observed that increased ghrelin level also strengthened the activation of the HPA axis and induced corticosterone release.[10] The effects of ghrelin on several stress-related disorders were intended to be described in this review by providing examples of rodent research that took into consideration the interaction of ghrelin with ghrelin receptors.

GHRELIN HORMONE

Ghrelin is an orexigenic hormone consisting of 28 amino acids that are released from the stomach into the bloodstream mainly in response to negative energy balance.[11,12] It is found in inactive form as deacylated ghrelin in human plasma, while acylated ghrelin with the help of the enzyme ghrelin O-acyltransferase (GOAT) is actively present.[13] GOAT is located in the endoplasmic reticulum of ghrelin-producing cells and provides acyl ghrelin (AG) formation by acylation of

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des-acyl ghrelin (DAG).[14] The resulting AG binds to the G-protein-bound ghrelin-specific receptor, that is, the growth hormone secretagogue receptor (GHSR). Stimulation of these orexigenic neurons increases food intake and regulates homeostatic feeding behavior to maintain energy balance.[15,16] The GHSR is mainly expressed in the arcuate nucleus (ARC) of the hypothalamus, which reveals the critical role of ghrelin in neuroendocrine and appetite-stimulating activities.[17,18] Plasma ghrelin levels increase before eating, decrease after eating, and gradually increase until the next meal.[19] However, GHSR is also expressed in various organs such as the hippocampus, ventral tegmental area (VTA), amygdala, anterior pituitary, adrenal and thyroid glands, pancreas, and heart.[20,21] Ghrelin hormone plays an important role in VTA's dopaminergic neurons, based on the reward mediated by GHSR[22], and in hedonic eating behaviors.[6,23]

EFFECTS OF GHRELIN ON APPETITE, REWARD, AND MOTIVATION

Ghrelin release leads to a decrease in energy consumption[24] and contributes to the storage of fatty acids in adipocytes.[25] In addition, Covasa and her colleagues[26] have predicted that ghrelin increases the number of meals and reduces the time difference between the two meals. Overduin et al.[27] also proved that the addition of ghrelin to cerebral ventricles on murine models resulted in an increase in food size and mealtime, thus regulating the eating behaviors of ghrelin[28] and also playing a role in the physiological mechanisms of obesity. Ghrelin injection enhances the desire to eat in humans[29] and induces rats to prefer fat-rich meals, according to animal studies.[30] Concurrently, it was discovered that providing ghrelin to healthy subjects evoked representations of the subjects' favorite food[31], and that this effect was amplified by presenting food photographs to the subjects.[32]

Hill and her colleagues[33] found a significant increase in ghrelin levels ($p<0,001$) of 71 obese women after a 12-month diet, suggesting that weight loss (due to diet) had an effect on increasing ghrelin levels. Thus, the increase in ghrelin plasma level also increases the feeling of hunger and food intake, explaining the reason for the repeated weight gain of patients after diet.[34] Control of food intake is provided by neuronal circuits located in both the hypothalamus and the brain stem. At the same time, food provides appetite-enhancing, rewarding signals regardless of metabolic needs.[35]

In addition to cortical areas, nutritional control has been found to have many processed nerve circuits, including the VTA, nucleus accumbens (NAcc), hippocampus, and mesolimbic regions involved in the modulation of amygdala eating behavior.[36]

Dopamine neurons in the mesolimbic region mediate the rewarding effects of food intake.[37,38] Dopamine plays an important role in regulating normal brain functioning such as behavior, learning, emotion, reward, and motivated behavior. The mesocorticolimbic dopaminergic system in the brain originates from the firing of dopaminergic cells starting from the VTA and extends from the NAcc to the prefrontal cortex. The VTA is the main region involved in both the selection of palatable foods and the motivational drive for regulating and attaining the rewarding properties of foods. Neuronal systems in the VTA have mesolimbic dopaminergic projections that are important for food reward and seeking.[39-41] With large amounts of ghrelin receptors expressed in the VTA of the mesolimbic system, ghrelin may be considered to play a key role in dopaminergic VTA-mediated reward signaling.[20,42]

The expression of GHS-R1a mainly in the ARC of the hypothalamus also indicates the critical role of ghrelin in neuroendocrine and appetite-stimulating activities. The GHS-R1a receptor, however, appears to have a function in both homeostatic control and neuronal circuits involved in reward and motivational aspects of food intake.[17,18,36] These findings suggested that ghrelin had an effect on hedonic eating behavior, prompting researchers to investigate its effects on food rewarding value and reward-based eating behavior. Ghrelin has been shown to boost the desire for rewarding meals such as high-fat diets and saccharin solutions.[30,43] In rats, it was seen that it preferably increased fat intake compared to carbohydrate intake after central ghrelin injection, thus proving that ghrelin has an effect on food preference.[30] In addition, it was observed that saccharin consumption increased after the application of ghrelin peripherally in mice, while this increase was not observed in GHS-R1a knockout mice.[43]

In another study, peripheral and centrally administered ghrelin increased the motivation for promoting sucrose rewards in a saturated rat, and by blocking the ghrelin signal, the response of hungry rats to sugar was reduced to the level of a saturated rat's response to sugar.[44] Operational conditioning was used to study the reward and motivational effects of ghrelin on food intake in such research.[45]

THE EFFECT OF GHRELIN ON STRESS AND STRESS-RELATED PSYCHIATRIC DISORDERS

Ghrelin interacts with the HPA axis, which is linked to stress reactions, in addition to controlling feeding behavior. Therefore, ghrelin also has a regulatory role in stress responses.[46] In one study, it was observed that plasma corticosterone concentration increased in rodents after systemic or central application of ghrelin, and cortisol concentration increased in humans.[47-49] There have also been studies that show that following central ghrelin administration, the amount of ACTH-producing cells in the pituitary increases.[48] As a result of studies that were carried out with the idea that the ghrelin system would increase the activity of the HPA axis, the blunt release of ACTH and corticosterone was observed after a short exposure to immobilization stress in ghrelin knockout mice.[50] On the other hand, it has become a question of how the activity of the HPA axis can affect the release of ghrelin. It has been shown that plasma ghrelin levels increase in humans by increasing cortisol levels with the application of an ACTH analog.[51] Based on these results, we can conclude that ghrelin is released in response to stress and is a hormone that acts in tandem with the HPA axis to mediate some stress-related behavioral changes.

There are also studies suggesting that the effects of exposure to acute and chronic stress on rodents on food intake and body weight are the role of ghrelin in stress-related nutritional behaviors. It was observed that acute stressors such as inactivity stress[52], novelty stress[53], as well as injection of lipopolysaccharide (LPS)[54] mostly reduced food intake. In addition, exposure of mice to a flooded cage for five days reduced their body weight[55], and similarly, the application of five days of social isolation[56] or chronic foot shock[57] also resulted in decreased food intake and decreased body weight. Although many other such studies have been carried out, we can conclude that ghrelin has distinct effects against various stressors, and its mechanism is still unknown. Although some research suggests that ghrelin reduces fear, anxiety, and depression-like behaviors in rodents, other research suggests the opposite. A recent study found that central administration of ghrelin antisense DNA reduced conditioned fear retrieval in unstressed rats and produced anxiolytic and antidepressant-like effects.[58] Similarly, Spencer and his team[50] showed that anxiety behaviors decreased in ghrelin knockout mice in basic conditions, but anxiety increased after acute immobilization stress, while another study found that ghrelin knockout mice showed higher levels of anxiety in non-stressful conditions.[59]

Genetic deletion of the GOAT enzyme and therefore attenuated AG levels[60] have also been shown to reduce anxiety-like behaviors before being exposed to stress.[59] Some studies to investigate the effects of AG and GHSR ligands have also produced contradictory results. Systemic or central injection of a single dose of AG has been shown to cause anxiety and depression-like behaviors in mice that have not previously been exposed to stress.[47,61,62] Similarly, it has been observed that the infusion of central ghrelin for a month increases anxiety and depression-like behaviors in rats.[63] However, ghrelin injection into the amygdala did not show a significant effect in fed mice, it was observed to have an anxiolytic effect only when there was no food.[64,65] Therefore, the effects of AG application are also thought to depend on nutritional status.

In conclusion one of the unique aspects of ghrelin is that it is an orexigenic hormone linked to food consumption, which fascinates researchers and motivates them to conduct extensive research on the hormone. Research on ghrelin increased when it was understood that ghrelin, which is often seen to promote food intake, has selectivity in food intake and the effect of seeing food as a reward and motivational source. It has been proven to affect dopaminergic regions in the brain, especially the amygdala, hippocampus, and NAcc, which provide reward, motivation, and hedonic eating control. The influence of ghrelin on nutritional behavior in healthy subjects discusses the effect of ghrelin on nutritional behavior by picking the meal that is more appealing to it amongst food alternatives and appetite. Furthermore, the ghrelin hormone is prominent in studies of stress and food consumption. The effects of the ghrelin hormone against stress were investigated because body weight change is linked to both stress and food intake. It has been observed that the HPA axis, which determines our responses to acute and chronic stress, can give different responses depending on the nutritional status as a result of injecting ghrelin into healthy subjects. In some studies, it was observed that the subjects exposed to stressors reduced food intake and their body weight decreased, while in some studies it was observed that administrating ghrelin activated the HPA axis by increasing the secretion of cortisol and ACTH. Based on the results of these studies, it can be clearly seen that stress exposure

affects the release of ghrelin, as well as the release of ghrelin. Ghrelin hormone, which has been shown to be affected by stress and alters release in case of stress, also plays a role in some disorders caused by stress. In a stress-free environment, however, anxiety behavior decreases in ghrelin knockout subjects, and anxiety status increases with stress application; thus, ghrelin knockout subjects show high anxiety levels in a stress-free environment. The ghrelin hormone has been shown to play a role in stress-related diseases, although no definitive judgment has been formed.

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