Review paper

Regulation of animal food intake and body weight by ghrelin: A review

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Abstract: Ghrelin is a gastric derived hormone composed of 28 amino acids. It is an endogenous ligand of the secretagogue receptor of growth hormone (GH). It regulates energy balance, stimulates eating and the release of growth hormone by transmitting information about peripheral nutritional status to the brain, and then regulates appetite, eating and body composition. It plays a role in obesity. It is essential to protect organisms from famine. The discovery of ghrelin has opened up many new prospects in neuroendocrine, metabolic and cardiovascular research, especially in obesity, indicating its possible clinical application. Recent research progress provides new clues for the multifaceted role of ghrelin in intracellular homeostasis. Ghrelin has the capacity to keep the intracellular environment while also overcoming metabolism in metabolic organs. This paper examines ghrelin's structure, receptor, and mechanism. Ghrelin's ability to regulate food intake; the relationship between ghrelin and obesity was discussed further, and the practical role of ghrelin in the treatment of diet-related diseases was discussed.

Keywords: Ghrelin; Feeding; Neuropeptides; Obesity

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1. Introduction

Dietary habits and dietary structure are one of the important factors affecting energy metabolism. Due to the interaction of genetic and environmental factors, an imbalance in energy metabolism leads to a large amount of fat being accumulated in the body, which leads to obesity. At present, more and more hormones and neurotransmitters have been targeted by studies to regulate food intake, such as ghrelin, peptide YY, cholecystokinin (CCK), insulin, etc. (Scott et al., 2013).

Ghrelin is an endogenous ligand of the growth hormone secretagin receptor (GHS-R) of growth hormone (GH) (Kojima et al., 1999). It is the only appetite-promoting peptide hormone known to be secreted in peripheral organs (Nakazato et al., 2001). Ghrelin can also stimulate gastric emptying and exercise, regulate sleep, improve taste, control glucose and fat metabolism, prevent muscle atrophy, and improve cardiovascular function (Luo et al., 2018, Vaccarino et al., 1985). Since ghrelin was discovered, a large number of studies have proved that it has unique functions in regulating energy homeostasis, especially in hypothalamic neurons involved in stimulating food intake (Yanagi et al., 2018). Fasting will increase ghrelin secretion, food intake will inhibit ghrelin secretion, and weight loss will also increase ghrelin secretion. Intraperitoneal in-

jection of acyl ghrelin could block the appetite-promoting effect of peripheral ghrelin on free-eating rats.

The identified ghrelin receptor is growth hormone secretagin receptor 1a (GHS-R1a). However, it has been confirmed that the ghrelin receptor is widely distributed, in which the expression is the highest in the pituitary, and it is found in other organs, including thyroid, heart, lung, liver, kidney, pancreas, stomach, spleen, intestine, adrenal gland, testis, and adipose tissue, hypothalamus, outer area of the hypothalamus, and metabolic organs (Kaiya et al., 2010).

There are great differences in the evolution of ghrelin receptors in mammals, birds, reptiles, amphibians, and fish. Different subtypes of ghrelin receptors are found in fish (20 species), and ghrelin receptor expression is also found in amphibians and birds. Through genome-wide technology, two ghrelin receptor subtypes were found in fish, including GHS-R1a and growth hormone secretagin receptor 2a (GHS-R2a) (Sakurai et al., 1998). Research shows that cypriniformes (such as goldfish, carp, and zebrafish) and silver carp (such as zebrafish) contain GHS-R1a and 2a at the same time, In addition, another ghrelin receptor subtype, GHS-R1a-like receptor (GHS-R1a-LR), was found for the first time in Mozambique tilapia and rainbow trout. Later, this receptor subtype was also found in spinous halibut, which is also a bony fish. Only GHS-R1a was discovered in mammals, birds, reptiles, and amphibians. The amino acid sequences of the two receptor subtypes have 70% homology (Kaiya et al., 2014). Ghrin and ghrin receptors in the hypothalamus can play a role in promoting appetite (Taylor et al., 2013).

2. Overview of Ghrelin

2.1 Ghrelin discovery and structure

In 1976, Bowers et al. found a weak and sustained release of methionine enkephalin derivatives in the anterior pituitary and named them growth hormone secretagogues (GHSs). In 1999, ghrelin, as a natural endogenous ligand of the GHSs receptor, was discovered by Kojima Kangyu and Kangawa, and its strong activity was detected in the stomach. Ghrelin is a protein composed of 28 amino acids and a gastric hormone. Its structural formula is shown in Figure 1, including 1 glycine (Gly), 4 serine (SER), 1 phenylalanine (PHE), 2 leucine (Leu), 4 proline (pro), 2 glutamate (Glu), 1 histidine (his), 4 glutamine (Gln), 2 arginine (ARG), 4 lysine (Lys) and 1 alanine (ALA). Ghrelin is secreted by X/A-like cells from the neck of the gastric fundus to the bottom of the oxygen-secreting gland. Its mRNA is highly expressed in gastric tissue and at a low level in the intestine, pancreas, kidney, and placenta. Gastric starvation is required for its synthesis. Ghrelin-o-acyltransferase (GOAT) mRNA is highly expressed in X / A-like cells of the stomach. The GOAT endoplasmic reticulum combines n-octyl coenzyme A with progrelin before transporting it to the Golgi to acylate progrelin, which is then transported to the Golgi and cleaved into ghrelin by PC1 / 3 (Schaeffer et al., 2013).

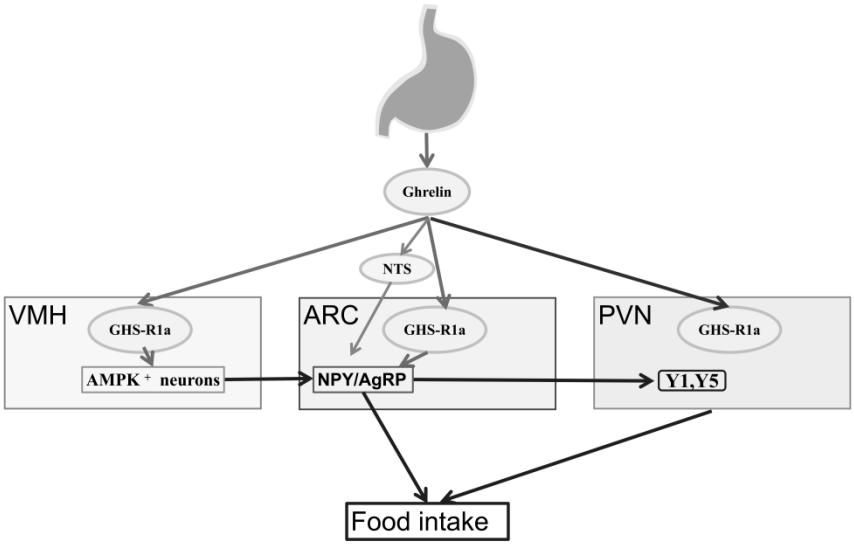

Figure1 Synthesis of Ghrelin and feeding signal pathway to hypothalamus

2.2 Ghrelin Mechanism

Ghrelin can play a role in hypothalamic neurons by binding to its receptor (also known as the ghrelin-GHS-R1a axis) to promote food intake in humans and rodents, leading to weight gain. It activates the neurons of neuropeptide Y (NPY) or agouti related protein (AgRP) through the vagal afferent nerve and blood circulation to induce feeding. Studies have shown that after vagal afferent nervous system resection, the increase in ghrelin level caused by fasting will disappear. GHS-R1a is transported to the stomach after it is combined into the nodal nerve of the vagus nerve. Ghrelin combines with GHS-R1a to produce an electrical signal. The electrical signal reaches the nucleus tractus solitarius (NTS), which is related to norepinephrine synthase. The axon terminal of norepinephrine synthase synapses with NPY neurons in the arcuate nucleus (ARC). NPY acts on Y1 and Y5 receptors in the paraventricular nucleus of the hypothalamus (PVN) to stimulate eating. Ghrelin in the blood circulation is transported through the blood-brain barrier and binds to neurons near the windowed capillaries in the median eminence (near the arcuate nucleus). By virtue of its vascular connection, the hypothalamus can directly sense peripheral signals and adjust the energy state accordingly (Srisai et al., 2017).The change trend of each index is shown in Table 1.

Table 1. The change trend between ghrelin and some index about food intake.

Index	Trend
Ghrelin	↑
GHS-R1a	↑
NPY	↑
AgRP	↑
POMC	↓
CART	↓
Food intake	↑

↑ means increasing; ↑ means decreasing

GHS-R1a mainly releases the ARC, ventromedial nucleus (VMH), and PVN in the hypothalamus. Ghrelin and other GHS can further enhance the activity of GHS-R1a by

stabilizing the conformation of GHS-R1a. The interaction between melanocortin receptor accessory protein 2 (MRAP 2) and GHS-R1a can enhance the G stimulated by ghrelin in AgRP neurons via Q signal transduction. Studies have shown that ghrelin can not induce food intake in mrap2 knockout (KO) mice. Ghrelin stimulates AgRP neurons and is an important endogenous regulator of ghsr1a function.-GHS-R1a axis is also involved in a variety of behaviors, including learning and memory, reward and impulse, anxiety, and so on (Hopkins et al., 2017).

Ghrelin-o-acyltransferase (GOAT) is the only known enzyme that catalyzes progrelin acyl modification. Its mRNA is mainly limited to the stomach and pancreas in human tissues, and is highly expressed in X/A-like cells producing ghrelin in the stomach. Because ghrelin plays a role in animal food intake, the ghrelin GOAT system has become an attractive research object. There is evidence that ghrelin plays an important role as a key regulator of glucose metabolism. Its physiological function is mediated by the GOAT. The enzyme can produce the active form of this metabolic hormone. GOATs may sense and communicate with the brain about the availability of peripheral nutrients to ensure effective metabolism and energy storage, which is essential to prevent hypoglycemia in famine. Long-term fasting will inhibit the acylation of ghrelin. Under this condition, the total level of ghrelin will increase, resulting in increased food intake (Yanagi et al., 2018).

GOAT is also located in the plasma membrane and transport vesicles of tibial bone marrow adipocytes. In the plasma membrane, GOATs use octanoic acid in bone marrow adipocytes to acylate deacylated ghrelin. GOAT mediated local acylation of exogenous deacylated ghrelin can activate GHS-R1a and then form fat in bone marrow (Frederich et al., 1995).

3. Ghrelin and the regulation of food intake and body weight

Weight regulation is regulated by a complex system, including peripheral and central factors. To maintain a stable weight, we need to balance food intake and energy consumption. Only when the energy intake is matched with the expenditure will the weight remain stable, which requires that the food intake or consumption must be strictly controlled. The endocrine signal is the primary factor that causes people to begin eating, and it also plays an important role in weight control and improving body fat distribution. Ghrelin, which plays an important role in food intake and weight regulation, is a hormone produced in the stomach and transmitted to the brain, especially the hypothalamus, in different ways. It has the characteristic of promoting appetite (Lin et al., 2010). Because the ghrelin system in obese patients is disturbed, it is very important to reveal their mechanism of action, which has aroused great interest (Allas et al., 2018).

3.1 effect of obesity on ghrelin's appetite-promoting effect

Prader-Willie syndrome is characterized by elevated circulating arginine levels and a relative lack of acylated ghrelin (also known as deacylated ghrelin) in obese patients. Acylated ghrelin analogues can improve human postprandial blood glucose levels and reduce waist circumference and fat mass (Stevenson et al., 2017). A recent study showed that reducing energy intake can inhibit ghrelin in obese women to promote weight loss.

Ghrelin can also be inhibited by low calorie diets, polyunsaturated fat-rich diets, and fructose supplementation (Kozimor et al., 2013).

Obesity impairs ghrelin's function in food balance and reward processing in the body, leading to a condition called ghrelin resistance. Obesity reduced ghrelin-stimulated growth hormone secretion. This effect was improved two weeks after gastric bypass (RYGB), but peripheral insulin sensitivity did not change. This suggests that the role of ghrelin in obesity is mainly characterized by central regulation rather than peripheral regulation (English et al., 2002). In a randomized controlled trial, Kalinowski et al. compared the effects of sleeve gastrectomy (SG) and RYGB on ghrelin, leptin, and glucose homeostasis. They found that ghrelin levels decreased after SG but increased after RYGB. However, metabolic improvement was not affected. In conclusion, the current study shows that one of the mechanisms of metabolic improvement caused by weight loss surgery may be the change in ghrelin level. Food restriction cannot inhibit the level of ghrelin in obese people, and this will damage the sense of satiety after meals, leading to overeating (Willesen et al., 1999).

3.2 Ghrelin regulates food intake and body weight in hypothalamus

Ghrelin activates hypothalamic AMP dependent protein kinase (adenosine 5 '-monophosphate (AMP) - activated protein kinase (AMPK) to perform its appetite promoting effect. Hypothalamic arc produces some key molecules regulating feeding behavior, including orexin NPY and AgRP, as well as anorexic opioid melanogen (POMC) and cocaine and amphetamine regulated transcription peptide (CART). GHS RS is expressed in 94% of NPY / AgRP neurons and 8% of POMC neurons (Hsu et al.,2015). Studies have shown that in tamoxifen induced AgRP creert 2 transgenic mouse model, selective re expression of GHS-R1a by NPY / AgRP neurons can restore ghrelin's appetite activity. NPY / AgRP neuron specific GHS-R1a knockout mice are resistant to diet induced obesity. Injection of ghrelin directly into ventral hippocampus (VHP) can stimulate feeding and activate orexin neurons in lateral hypothalamus (LHA). This effect can be cancelled by orexin antagonist central pretreatment (Denis et al., 2015). The appetite promoting effect of ghrelin on NPY / AgRP neurons is limited to mice fed with non delicious food, and these neurons are dispensable when there is very delicious food (Sun et al., 2004).

Exogenous ghrelin can effectively affect human food intake and weight gain. Long-term and short-term hormone signals from the periphery act on the central nervous system and affect eating behavior. The main areas involved are the hypothalamus, especially the arcuate nucleus, and the dorsal complex of the vagus nerve in the brain stem. The arcuate nucleus integrates signals from the periphery and brain stem. They are also regulated by long-term body energy storage signals such as leptin and insulin (Kojima et al., 1999).

3.3 Ghrelin promotes appetite and weight gain through the extrahypothalamic area

Ghrelin was originally isolated from the stomach, but ghrelin was also identified in other peripheral tissues, such as the gastrointestinal tract, pancreas, ovary, and adrenal cortex (Cowley et al., 2003). In the brain, ghrelin-releasing peptide producing neurons

have been identified in the pituitary, hypothalamic arcuate nucleus, and a group of neurons adjacent to the third ventricle between dorsal, ventral, paraventricular, and arcuate hypothalamic nucleus (Mayte et al., 2012).

In addition to the hypothalamus, ghrelin also promotes appetite through LHA (including hippocampus, amygdala and ventral tegmental area (VTA)) and leads to weight gain. LHA is a region that controls energy balance and motivational behavior. It produces two appetite promoting neuropeptides: orexin and melanin concentrating hormone. LHA is directly related to arc, PVN and VTA. In this appetite promoting effect, the role of neurons is necessary. Ghrelin needs to combine with these neurons in order to play a follow-up role. Moreover, these outer areas of hypothalamus are also closely related to the function of dopamine system and control the motivation of a variety of behaviors, such as hedonic eating (Sakurai et al., 1998).

In conclusion, ghrelin-GHS-R1a signal directly regulates body weight by activating NPY / AgRP neurons to induce feeding, and indirectly regulates food intake through vhp-lha-vta pathway.

4. **Regulation of ghrelin secretion mediated by external factors**

The level of ghrelin secreted by the stomach largely depends on the nutritional status (Cummings et al., 2001). In addition, ghrelin levels show diurnal changes and seem to be affected by age, gender, body mass index, growth hormone, glucose and insulin. Notably, leptin is also thought to have an effect on circulating ghrelin levels. It is speculated that the satiety inducing effect of leptin includes inhibiting ghrelin secretion (Yildiz et al., 2004).

4.1 Regulation of nutrients on ghrelin secretion

Ghrelin levels increased before eating and decreased after eating, which is due to the influence of nutrients in food. Nutrients such as glucose, lipids, amino acids, and trace elements ingested by animals will affect the ghrelin level in animals.

4.1.1 Glucose's Ghrelin-Regulating Effect

Ghrelin plays an important role in glucose homeostasis. Glucose is an important substance that regulates the level of ghrelin in the body. It showed that ghrelin inhibits glucose-sensing neurons in the hindbrain. In humans and other mammals, ghrelin levels rise before meals and decline rapidly after ingestion. When the insulin level was low, the increase in ghrelin level and the decrease in glucose level overlapped in time. In different glucose environments, various glucose transporters, channels, and enzymes that regulate glucose response may participate in regulating Ghrelin secretion (Wang et al., 2008).

4.1.2 Effect of trace elements on Plasma Ghrelin Level

The lack of trace elements is one of the important factors leading to anorexia in children, and trace elements also have an impact on the level of ghrelin in the body, especially copper and zinc. Studies have shown that copper and zinc can significantly increase the level of plasma ghrelin (Yang et al., 2012). Therefore, the study of ghrelin and trace elements can provide new ideas for the study of anorexia in children.

4.2 Hormone regulation of ghrelin secretion

4.2.1 Somatostatin (SS) effect on ghrelin secretion

SS, also known as growth hormone releasing inhibitory hormone, is a drug suitable for acute gastric ulcer bleeding, bleeding caused by erosion and hemorrhagic gastritis, severe acute esophageal variceal bleeding, treatment of pancreaticobiliary and gastrointestinal disorders, acute pancreatitis, and prevention of postoperative complications of the pancreas. It will inhibit ghrelin secretion in a paracrine manner, which leads to a reduction in food intake. After observing the effect of SS on the level of serum ghrelin in patients with severe acute pancreatitis, it was found that the level of serum ghrelin in patients injected with SS decreased (Barkan et al., 2003).

4.2.2 Insulin's effect on ghrelin secretion

The discovery of ghrelin has opened up many new prospects in neuroendocrine, metabolic, and cardiovascular research, indicating its possible clinical application. After an insulin injection, the level of ghrelin in plasma will decrease and eventually lead to a reduction in food intake. This may be because insulin will resist and affect the ability of fructose to increase the level of ghrelin in the form of hormone activity. In mice, rats, and humans, as well as in islets of Langerhans, ghrelin can inhibit insulin release.In cells, the signal transduction mechanism of the ghrelin receptor is very unique. Different from the mechanism used to release growth hormone, ghrelin attenuates glucose-induced cAMP production, thereby driving the activation of voltage-dependent potassium channels and inhibiting glucose-induced islet cell [Ca2+] increase and insulin release. In vitro, pharmacological and genetic inhibition of islet-derived ghrelin significantly increases glucose-induced insulin release (Dezaki et al., 2004). Islets express ghrelin, GHS-R1a, and GOAT (Date et al., 2002). In obesity models with high fat, diet-induced leptin deficiency, knockout of ghrelin, GHS-R, or GOAT can enhance insulin release and prevent impaired glucose tolerance. Therefore, manipulating the insulin inhibitory function in the ghrelin-GHS-R system, especially in islets, can optimize insulin release to meet systemic needs. When insulin demand exceeds the physiological range (including insulin resistance or obesity), the antagonism of ghrelin function can promote insulin secretion, thereby preventing glucose intolerance. The antagonistic action of ghrelin provides a new strategy for the treatment of type 2 diabetes with impaired insulin release (Ghatei et al., 1983).

4.2.3 The relationship between the levels of leptin and ghrelin

Leptin and ghrelin are two hormones considered to have important effects on energy balance. In obese subjects, circulating levels of leptin increased, while ghrelin levels decreased. In fact, the effect of leptin on energy homeostasis is the opposite to that of ghrelin (although not complementary). Leptin induces weight loss by inhibiting food intake, while ghrelin is an appetite-stimulating signal. Tschop et al. demonstrated that the fasting plasma ghrelin level in obese patients was negatively correlated with the fasting plasma leptin level (Tschöp et al.,b2001).

Leptin acts in a similar manner to SS, inhibiting ghrelin secretion. Injection of leptin resulted in decreased ghrelin secretion, reduced food intake, and weight loss. Leptin can

directly inhibit the expression of gastric ghrelin in rats in a dose-dependent manner. Under fasting, the expression level of gastric ghrelin mRNA increases, partly due to the reduction of leptin levels in the gastric fundus. The results collected so far show that leptin and ghrelin have different effects on the production of various orexins and orexins in hypothalamic neurons, resulting in more or less opposite effects on energy balance. Huo et al. found that a large proportion of leptin-responsive neurons in the medial nucleus tractus solitarius (mNTS) were activated by gastric dilation, which is physiologically meaningful because leptin acts directly on neurons in the mNTS and is used to reduce food intake through interaction with gastrointestinal signal processing (Huo et al., 2007). In addition, Schwartz et al. showed that injection of leptin into the third ventricle significantly increased the response of NTS neurons to gastric load, while injection of NPY into the third ventricle decreased the efficacy and efficiency of gastric load to activate NTS neurons (Schwartz et al., 2002).

5. Prospect and Summary

Ghrelin is produced by the stomach and transmitted to the hypothalamus through two routes (vagal afferent nervous system and blood circulation). Ghrelin not only plays a role through the hypothalamus, but also plays an appetite-promoting role through the outer areas of the hypothalamus. Ghrelin must combine with neurons in these outer areas to play an appetite-promoting role. It is a potential target for regulating body weight. Excessive food intake and high body weight will damage the function of ghrelin in the body. Ghrelin not only regulates appetite but also plays an important role in type 2 diabetes, Parkinson's and inflammation. Many factors will affect ghrelin secretion, which then affects food intake. The GOAT may serve as a target in therapeutic interventions that regulate body weight and glucose metabolism.

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