Ghrelin: Are its Levels Related to Obesity?

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ABSTRACT: Ghrelin, a recently discovered hormone, has been found primarily in the stomach, though it exists in other areas of the body as well. While researching ghrelin levels, scientists found that the hormone increases feeling of hunger when it is increased in the body. In addition, high levels of ghrelin have been found to suppress the amount of fat used by the adipose tissue. In man it plays a role in energy homeostasis and somatotropic function. However, when the energy balance gets disturbed (energy intake > energy expenditure), this may eventually lead to sustained weight problems, like for example, in obese subjects. Obesity is an excess of body fat mass. It has become an international public health problem. Unfortunately, effective treatment options are limited.

In this review it is summarized the available data, concerning the hormone ghrelin that seems to influence the development of obesity, through its role in control of energy balance, food intake and regulation of body weight. Ghrelin is an anabolic hormone and its levels change profoundly in obesity, suggesting that this is an important hormone in body weight regulation.

Key Words: Ghrelin, Body weight regulation, Obesity.

1. INTRODUCTION

In most humans, body weight is maintained in a stable condition. Humans can have the same body weight for many years, if the energy intake is equal to energy expenditure (energy balance). However, when the energy balance gets disturbed, this may lead to sustained weight problems, like in obese subjects.

In the developed and developing world, levels of obesity and its related disorders are increasing at a rate that could be considered of epidemic proportions. For this reason, the last years there is a significant increase in the knowledge of the physiological and molecular mechanisms regulating body mass.

There are numerous peptides involved in the regulation of energy homeostasis, some of which are produced centrally and others peripherally in the gastrointestinal tract, with some produced at both locations. These peptides have come to be known as members of the “gut-brain axis”. Interestingly, only one peripheral hormone, ghrelin, has been discovered that stimulates appetite, while many others inhibit appetite. As ghrelin effects on a large number of physiological functions, it may be involved in the pathomechanism of several human disorders, including disturbances of appetite, energy homeostasis and body weight.

The purpose of this review is to summarize the data about the role of ghrelin in the pathogenesis of human obesity. Thus the change levels of ghrelin and the identification of the molecular mechanisms mediating ghrelin effects on feeding, may provide new therapeutic targets for obesity.

2. THE HORMONE GHRELIN

2a. What is ghrelin?

Ghrelin, a peptide hormone, was first described by Japanese researchers in the journal Nature in December 1999. They chose the name “ghrelin” because “ghre” is the Proto-Indo-European root of the word “grow”, and ghrelin also stimulates the pituitary gland to release growth hormone. The majority of circulating ghrelin is released from the endocrine cells of the stomach mucosa (these cells have been identified as the X/A cells).
It was discovered as part of a study to identify the previously unknown endogenous ligand for the growth hormone secretagogue receptor (GHS-R). It was known that this receptor was stimulated by synthetic growth hormone-releasing compounds.

Ghrelin is synthesized as a preprohormone (117-amino-acid peptide), then proteolytically processed to yield a 28-amino acid peptide. An interesting modification is imposed on the hormone during synthesis in the form of an n-octanoic acid bound to one of its amino acids (acyl ghrelin, called “simply ghrelin”). This modification is necessary for biologic activity. Ghrelin has a unique acid chain on its N-terminal end.

However, the majority of circulating ghrelin is actually lacking this acyl group and is known as des-acyl or des-octanoyl ghrelin (> 90%). This may due to the shorter half-life of ghrelin than that of des-acyl ghrelin (it binds to the CHS-R in the tissues). Deacylation of ghrelin to des-acyl ghrelin is also responsible for the reduced half-life of ghrelin.

Recent developments have shown that ghrelin gene can generate various bioactive molecules besides ghrelin. These molecules can be classified in three main groups: ghrelin and analogs, C-ghrelin and obestatin. All molecular forms of ghrelin were found in human plasma as well as in the stomach, but major active forms see to be acyl ghrelin and des-acyl ghrelin.

Ghrelin peptide was originally isolated from the stomach, but ghrelin protein has also been identified at lower levels in other tissues, such as the gastrointestinal tract, pancreas, adrenal cortex, ovary, placenta, fallopian tube, testis, prostate, liver, gall bladder, breast, thyroid, spleen, human lemphocytes, lung, kidney, skeletal muscle, myocardium, vein and skin.

Ghrelin produced in tissues other than gastrointestinal tissues may have a range of still-unidentified physiological autocrine or paracrine effects (GHS-R1a expression is also detected in many of these tissues).

In the brain, ghrelin-producing neurons have been identified in the pituitary, in the hypothalamic arcuate nucleus (ARC) and in a group of neurons near to the third ventricle, between the dorsal, ventral, paraventricular and arcuate hypothalamic nuclei.

These neurons terminate on Neuropeptide Y (NPY), Agouti-related protein (AgRP), Proopiomelanocortin (POMC) and Corticotrophin-relasing hormone (CRH) neurons, forming a circuit which could mediate in energy homeostasis. Recently, Sato et al. characterized ghrelin within the rat hypothalamus. The physiological role(s) of ghrelin secreted from the hypothalamus, however, remains unclear.

### Table 1. Regulators of circulating Ghrelin.

<table>
<thead>
<tr>
<th>Effect on circulating Ghrelin</th>
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<tbody>
<tr>
<td>Food intake ↓</td>
</tr>
<tr>
<td>Age ↓ With increasing age</td>
</tr>
<tr>
<td>Gender Higher in females compared to males</td>
</tr>
<tr>
<td>BMI ↓ With increasing BMI</td>
</tr>
<tr>
<td>GH ↓</td>
</tr>
<tr>
<td>Glucose ↓</td>
</tr>
<tr>
<td>Insulin ↓</td>
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*BMI: Body Mass Index  GH: Growth Hormone*

(From Klok MD et al 2006)

2b. Secretion and regulation of ghrelin levels

The secretion of ghrelin by the stomach depends largely on the nutrition state. Ghrelin levels show preprandial increases and postprandial decreases. In addition, ghrelin levels show a diurnal variation that is influenced by various factors (age, gender, body mass index, growth hormone, glucose and insulin (see Table 1).

Furthermore, leptin influence the circulate ghrelin levels. It has been suggested that the satiety-inducing effects of leptin suppress the secretion of ghrelin.

Circulating ghrelin levels are increased by fast-
ing and energy restriction and decreased by food intake\textsuperscript{2,16,23}. In fact, circulating ghrelin levels are increased in anorexia and cachexia, reduced in obesity and restored by weight recovery\textsuperscript{* 16}. These changes are opposite to those of leptin and it has been suggested that these hormones signal the metabolic balance and manage the neuroendocrine and metabolic response to starvation\textsuperscript{24,25}.

Insulin also has a temporal relationship with ghrelin concentrations. Insulin levels rise, as ghrelin levels fall.

Free fatty acids are suggested to reduce ghrelin levels in human\textsuperscript{26} as well as glucagon, that reduce ghrelin levels by a pituitary-dependent mechanism\textsuperscript{27,28}.

Secretion of ghrelin in the hypothalamus is highly regulated by nutritional status such as feeding, fasting and exposure to a high fat diet. Recent studies show that the metabolism of hypothalamic fatty acid mediates the orexigenic action of ghrelin\textsuperscript{29}. In the context of food deprivation, the increased ghrelin levels promotes feeding through AMP-dependent protein kinase which mediate to the modulation of hypothalamic fatty acid metabolism.

2c. Receptors

The effects of ghrelin are mediated via the growth hormone secretagogue receptors (GHSR) that are expressed by neurons in the arcuate nucleus and the ventromedial hypothalamus.

The ghrelin receptor was known before ghrelin was discovered. It was named growth hormone secretagogue receptor (GHS-R) because, when is activated potently, stimulates secretion of growth hormone. The natural ligand for the GHS-R was announced as ghrelin.

The ghrelin receptor is a G protein-coupled receptor, with two variants that are designated, type 1a (GHS-R1a) and type 1b (GHS-R1b)\textsuperscript{11}. GHS-R1a is highly expressed in the hypothalamus, the pituitary\textsuperscript{32} and also in other areas of the CNS\textsuperscript{33}. The role of GHS-R1a is to control appetite, food intake and energy balance. Recent experiments showed that GHS-R1a is essential for the stimulatory effects of ghrelin on GH secretion, as well as its orexigenic effects\textsuperscript{34}. Additionally, they show that the acylation of ghrelin at Ser3 is necessary for GHSR activation\textsuperscript{35} and for crossing of the ghrelin the blood-brain barrier\textsuperscript{36}.

Figure 1. Ghrelin reaches the hypothalamus via three different pathways. (From Korbonits M, et al 2004).

So, des-acyl ghrelin does not bind GHS-R1a and its effects should be mediated by other receptors, specific for des-acyl ghrelin, or by receptors common to acyl and des-acyl ghrelin (non of this have been characterized yet).

2d. How ghrelin exerts its effects

The peripheral ghrelin is released from the gastrointestinal tract (GI) and it is believed that it is come into the brain through three mechanisms (Figure 1)\textsuperscript{37}:

a) directly, via the blood stream, to enter the anterior pituitary and other areas of the brain not protected by the blood brain barrier (BBB)\textsuperscript{38}.

b) directly by crossing the BBB.

c) indirectly, via the vagus nerve\textsuperscript{39}.

Ghrelin acts in the arcuate nucleus, a very important area in the regulation of feeding and appetite\textsuperscript{38,40} and also causes neuronal activity in the paraventricular nucleus, the lateral and dorsomedial hypothalamus, the area postrema, and in the nucleus of solitary tract.

In the ARC nucleus are found GHS receptors, on neurons that release NPY and AgRP peptides (potent stimulators of weight gain)\textsuperscript{41}, where ghrelin acts. GHS-R can be found on presynaptic nerve endings

\textsuperscript{* Orexigenic actions of ghrelin are extremely rapid and short-lived, as required for a signal influencing individual meal-related behavior\textsuperscript{44,45}.}
and influence the release of the transmitter. As well the researchers found, ghrelin promotes appetite in two ways (Figure 2):

a) directly, by depolarizing the orexigenic neurons NPY/AgRP.

b) indirectly, by increasing the tonic inhibition, exerted by the NPY/AgRP neurons over the anorexigenic POMC/CART (cocain-amphetamine related transcript) neurons.

2e. Effects of ghrelin

Ghrelin was identified via its growth-hormone releasing effect. In addition to this effect, ghrelin exerts a wide spectrum of endocrine and nonendocrine actions, as: orexigenic effect, coupled with control of energy expenditure, control of gastric motility and acid secretion, influence on both endocrine and exocrine pancreatic function and on glucose metabolism, stimulation of lactotroph and corticotroph secretion, inhibition of gonadal axis, cardiovascular actions, influence on behavior and sleep, on bone physiology, modulation of cell proliferation and apoptosis.

Ghrelin, as an orexigenic factor* was considered triggering meal initiation, but it is not yet clear whether it is directly related to the rise in ghrelin levels. As Theande-Carrillo et al. suggested that the well known pre-meal peaks of circulating ghrelin are triggering preparation processes in the CNS rather than actually initiating meals. Moreover, Sat et al. indicated that ghrelin is not critical for feeding performance.

The primary effect of ghrelin injections on meal patterns is to decrease the latency to feed. Thus ghrelin increase meal number without affecting meal size. Ghrelin stimulates also gastrointestinal motility, gastric acid secretion and pancreatic exocrine secretion. All these functions prepare the gastrointestinal tract for effective transport and processing of food. Ghrelin administration increases also the enzyme activity of numerous lysosomal hydrolases, possibly helping the body prepare to digest nutrients. Ghrelin also increases RQ in obese humans. This suggests that this protein regulates substrate utilization and may promote metabolic flexibility.

The peripheral ghrelin signal the status of energy balance to the central nervous system and promotes food intake through the activation of the hypothalamic orexin neurons, neuropeptide Y-Y1 receptor pathway and over-expressing the agouti-related protein.

In addition to those effects, ghrelin has been also implicated on the regulation of lipid metabolism, with effects in the liver, skeletal muscle and adipose tissue. Ghrelin stimulates lipogenesis in differentiated adipocytes in vitro and in vivo, by increasing the levels of peroxisome proliferator-activated receptor a and the insulin-induced glucose uptake. Also ghrelin antagonizes lipolysis reducing isoproterenol-stimulated lipolysis in vitro and stimulates the proliferation and differentiation of preadipocytes.

The central ghrelin and NPY mRNA levels are significantly higher in the hypothalamus in obese compared to lean subjects. This suggests an important role for a central ghrelin in the pathogenesis of obesity in humans.

3. GHRELIN AND OBESITY

It is still not clear if abnormalities in ghrelin system is the cause or a consequence of obesity. In obese humans circulating ghrelin levels are negatively correlated with percentage body fat and BMI and are therefore lower in obese subjects than in normal body.
weight controls. Obese humans show also, a disturbed diurnal variation in ghrelin levels. 

Ghrelin is linked to obesity in two ways:
a) through its short-term (day to day, meal to meal) effects on hunger and meal initiation.
b) through its long-term (year to year) control of energy balance.

In essence ghrelin makes people eat more than they need to and makes them store calories as fat. Ghrelin makes also very difficult to maintain diet-induced weight loss, because its levels show an increase, as if to compensate for this weight loss.

It is thought that ghrelin is linked to excessive food intake in two ways:
a) the postprandial reduction* in ghrelin levels may increase the time for which the subject feels hungry.
b) the elevated ghrelin levels may not reduced the speed of gastric emptying and the feeling of satiety not elicited. So, without the feeling of satiety obese humans eat more than they need and thus gain weight.

Furthermore, in obesity, the lower ghrelin levels may increase the use of fats as a metabolic fuel. Actually, Tschöp et al. found that ghrelin regulates the body’s choice of metabolic substrate. Actually, recent studies show that the orexigenic action of ghrelin, results from the fatty acid metabolism in hypothalamus. However, as body weight is reduced, the ghrelin levels are increased, reducing the use of fat as metabolic fuel and more fat is conserved and stored.

Obese humans do not lose their responsiveness to ghrelin, but may be are oversensitive to this, for example, because of an overexpression of the GHS-R. In fact, it has been shown that a low-dose infusion of ghrelin increased the energy intake in obese people and not in lean people. In addition, a high-dose infusion with ghrelin led to a higher increase in food intake in obese patients compared with lean subjects.

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* In human subjects, plasma ghrelin levels increase nearly two fold immediatly before meals and fall within 1h after eating.

* Intact β-adrenergic signaling is required for the ghrelin-induced increase in body weight gain. In human subjects, plasma ghrelin levels increase nearly two fold immediatly before meals and fall within 1h after eating. (See Figure 3).

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Many studies have been performed to investigate ghrelin as therapeutic target for obesity treatment. In a study with rats it was demonstrated that anti-ghrelin blocks ghrelin-induced increase in food intake after ghrelin injection.

In addition, the ghrelin receptor is another potential drug target. It has been demonstrated that GHS-R antagonists result in a decrease of energy intake in lean and obese mice. However, as it is possible, the ghrelin system functions differently in humans, more research is still necessary.

One other strategy is to target genes that are involved in ghrelin functioning. That is the use of agents that stimulate inhibitors of ghrelin signaling, in order to suppress ghrelin’s stimulatory effect on food intake and body weight.

Furthermore, the peptide ghrelin constitute possible target for therapeutic intervention. Makimura et al. demonstrated that a reduction of hypothalamic AgRP results in an increase of metabolic rate and a decrease of body weight, without affecting food intake in mice. This suggests that agents antagonizing the effect of AgRP may be a useful strategy to treat obesity.

The researches also suggest, that the size, the composition* of a meal and the frequency of meals have

* Lipids suppress ghrelin levels less effectively than carbohydrates or proteins do.
significant effects on ghrelin levels and consequently on development of obesity\textsuperscript{67,68,69}. It is important for obese humans to follow a specific diet in order to regulate food intake and body weight.

4. CONCLUSION

Since its discovery in 1999, ghrelin has become one of the most important subjects of scientific research. This is due to the multiple functions of ghrelin actions such as the metabolic effects and various others, including the cardiovascular, endocrine and immunological ones.

Ghrelin is believed that it is involved in short-term and long-term regulation of energy balance, control of appetite, selection of metabolic substrates, stimulation of gastric acid secretion and regulation of gastrointestinal tract motility. It produces these effects in the hypothalamus, directly through activating the AgRP/NPY neurons and also indirectly through inhibiting the POMC/CART neurons.

The functions and the effects of ghrelin have been well documented, but the mechanisms that regulate its release are less well understood.

Ghrelin is linked to obesity, because makes people to eat more than they need, to store excess calories as fat and to make difficult to maintain diet-induced weight loss. So, increasing the possibility that blockade of ghrelin action (with ghrelin-receptor antagonists) might promote weight loss in obese individuals. Furthermore, ghrelin antagonists may, in future, have a powerful role to play in the medical management of obesity. However, Lu et al.\textsuperscript{70} have been reported that antagonizing the peripheral ghrelin pathway alone, may not be effective for treating obesity. Combination therapies that block multiple orexigenic pathways may be needed to evaluate the anti-ghrelin therapies.
REFERENCES


hypothalamic circuit regulating energy homeostasis.


