ROLE OF HUNGER HORMONE: GHRELIN

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ABSTRACT
Ghrelin was discovered as a peptide hormone that potently stimulates growth hormone release from the anterior pituitary, as demonstrated in rats, humans and pigs. Ghrelin has emerged as the first identified circulating hunger hormone. Ghrelin and synthetic ghrelin mimetics (the growth hormone secretagogues) increase feed intake and increase fat mass by an action exerted at the level of the hypothalamus. There is also strong evidence that ghrelin has a peripheral appetite modulatory effect on satiety by affecting the mechanosensitivity of gastric vagal afferents, making them less sensitive to distension resulting in over eating. Circulating ghrelin levels depend on acute and chronic changes in energy balance, fasting increasing and feeding decreasing its concentrations. It is found that plasma ghrelin levels in the cow are reduced 1 h after feeding and return to prefeeding levels within 4 h. In fetuses, it seems that ghrelin is produced early by the lung and promotes growth. Animal model indicate that ghrelin may enter the hippocampus from the bloodstream, altering nerve-cell connections, and so enhancing learning and memory. Given the effects of ghrelin on energy metabolism and hunger, it is a prominent target for development of anti-obesity treatment. Recently, research scientists have developed an anti-obesity vaccine, which is directed against the hormone ghrelin in rodents and pigs. Further studies are needed to understand the physiological and pathological roles of ghrelin cells in both small and large intestines. Moreover, post-transcriptional modifications are very important for physiological active ghrelin, necessitate the need to understand how ghrelin-o-acyl transfersae (GOAT) is involved in the regulation of ghrelin biosynthesis and consequently may be important for controlling ghrelin cells in some physiological states.

KEYWORDS: ghrelin, feed intake, learning and memory.

INTRODUCTION
The discovery of ghrelin was reported by Masayasu Kojima and colleagues in 1999. Ghrelin was discovered as a peptide hormone that potently stimulates growth hormone release from the anterior pituitary, as demonstrated in rats (Kojima et al., 1999, Seoane et al., 2000), humans (Peino et al., 2000, Takaya et al., 2000) and pigs (Salfen et al., 2004). The name is based on its role as a growth hormone-releasing peptide, with reference to the Proto-Indo-European root ghre, meaning to grow. The name can also be viewed as an interesting (and incidental) pun, too, as the initial letters of the phrase growth hormone-releasing give us “ghre” with “lin” as a usual suffix for some hormones.
small number of neurons located in the arcuate nucleus. Ghrelin is also produced in the hypothalamic arcuate nucleus, where it stimulates the secretion of growth hormone from the anterior pituitary gland (Mondal et al., 2005). Receptors for ghrelin are expressed by neurons in the arcuate nucleus and the lateral hypothalamus they are also found in the heart, and adipose tissue. Ghrelin levels increase before meals and decrease after meals. It is considered the counterpart of the hormone leptin, produced by adipose tissue, which induces satiation when present at higher levels. In addition, evidence from many species indicates that ghrelin exerts a variety of actions, affecting energy balance (Horvath et al., 2001), gastrointestinal motility and secretion (Masuda et al., 2000) and feeding behaviour (Wren et al., 2000). The central orexigenic effects of ghrelin are independent on growth hormone stimulation and appear to be mediated, at least in part, through activation of neuropeptide Y/agouti-related peptide hypothalamic neurons (Horvath et al., 2001). Administration of exogenous ghrelin increases neuropeptide Y gene expression and blocks leptin-induced feeding reduction, thus implying a possible competitive interaction between ghrelin and leptin in feeding regulation (Nakazato et al., 2001).

**FORMS**

Ghrelin exists in an endocrinological inactive (pure peptide) and an active (octanoylated) form. Interestingly, ghrelin was found to be present as two molecular forms: acyl-ghrelin modified with medium chain fatty acids and des-acylated-ghrelin lacking side chain modification (Kojima et al., 1999). Although acyl-ghrelin is only known to bind to GHS-R (Falls et al., 2006) accumulating results have shown that des-acylated-ghrelin has various physiological functions via unknown specific receptor, including involvement in cell death, feeding behavior, and energy and glucose homeostasis (Baldanzi et al., 2002, Fujimiya et al., 2008).

**SYNTHESIS AND STRUCTURE OF GHRELIN AND ITS RECEPTOR**

Ghrelin is synthesized as a prohormone, which is then proteolytically processed to yield a 28-amino acid peptide. A unique modification is imposed on the hormone during biosynthesis in the form of n-octanoic acid bound to the Ser-3 residue by ghrelin O-acyltransferase (GOAT). The acylation is essential for its orexigenic and adipogenic effects or biologic activity. Such acylation is thought to be critical for transport across the blood–brain barrier, receptor binding and overall bioactivity (Muccioli et al., 2001, Banks et al., 2002). The major site of ghrelin production is the stomach mucosa (Date et al. 2000, Tomasetto et al. 2000, Rindi et al., 2002), whereas lower amounts derive from small and large intestine, pancreas, kidney, immune system, placenta, pituitary, testis, ovary and hypothalamus (Casanueva and Dieguez, 2002). With the possible exception of mouse, ghrelin cells have been demonstrated to be independent from somatostatin (D), serotonin (enterochromaffin, or EC) and histamine (enterochromaffin-like, or ECL)-producing cells (Date et al. 2000, Rindi et al., 2002), and comprise P/D1-type cells in human, A-like cells in rat and X cells in dog (Rindi et al., 2002). In all species, ghrelin cells have been consistently revealed to be closed-type endocrine cells, with no contacts with the lumen (Rindi et al., 2002), in keeping with the indirect mechanisms of stimulation of ghrelin secretion. Ghrelin structurally resembles motilin and they share about 21% amino acid identity and their receptor also has structural similarity with 44% similarity in amino acids, indicating that they comprise a motilin-ghrelin family (De Smet et al., 2009). Although acyl-ghrelin is only known to bind to GHS-R (Falls et al., 2006), accumulating results have shown that des-acylated-ghrelin has various physiological functions via unknown specific receptor, including involvement in cell death,
feeding behavior, and energy and glucose homeostasis (Baldanzi et al., 2002, Fujimiya et al., 2008). The ghrelin receptor is a G protein-coupled receptor, formerly known as the GHS receptor (growth hormone secretagogue receptor). Cells within the anterior pituitary bear a receptor that, when activated, potently stimulates secretion of growth hormone. Ghrelin receptor has also been identified as being expressed in vagal afferent cell bodies as well as the vagal afferent endings throughout the gastro-intestinal tract (Page et al., 2007).

Ghrelin's activity in modulating feeding behavior and energy balance are best explained by the presence of ghrelin receptors in areas of the hypothalamus long known to be involved in appetite regulation. Receptors are also found concentrated in other areas of the brain, including the hippocampus and regions known to be involved in reward systems (e.g. tegmental area); indeed, ghrelin appears to activate some of the same circuits that are involved in drug reward, which may also be related to this hormone's effects on appetite.

**Figure:** Localization of ghrelin-immunopositive cells in the stomach (rodents, avians, amphibians and fish). (a) Ghrelin cells in the rat stomach. Ghrelin cells are mainly observed from the glandular base to the body of the fundic gland, and gastric ghrelin cells in the rat have been clarified to be closed-type cells. Ghrelin cells are scattered throughout the mucosal layer in (b) the proventriculus of the chicken and (c) bullfrog stomach, and those ghrelin cells are also closed-type cells as rodents. (d) Ghrelin cells in the trout stomach are localized in the mucosal layer, and both closed- and opened-type cells are found in the trout. Scale bars = 100 μm in (a), (c), (d); 30 μm in (b).

In rodents, ghrelin-producing cells were observed in all regions of the gastrointestinal tract: gastric body, antrum, duodenum, ileum, cecum, and colon. Ghrelin-producing cells were most dense in the gastric body (Figure (a)) and were found in the mucosal layer but not in the myenteric plexus in all of the examined regions. In nonmammalians, it has been confirmed that ghrelin mRNA is abundantly expressed in the stomach (Kaiya et al., 2001, Kawakoshi et al., 2007). In avians, ghrelin-immunopositive cells were found in the mucosal layer of the proventriculus (Figure (b)) that corresponds to a first glandular part of the stomach in which digestive enzymes are mixed with food before the gizzard (Wada et al., 2003). However, ghrelin immunoreactivity in avians was not located in the myenteric plexus, and many more ghrelin-immunopositive cells were found in the middle layer than in the base of the mucosal layer, with the majority of ghrelin cells being round-shaped and closed-type cells (Wada et al., 2003). Features of gastric ghrelin cells in amphibians and reptiles are similar to mammals or avian ghrelin cells. Ghrelin cells in these animals were also found in the gastric mucosal layer but not in the myenteric plexus or muscle layers of the stomach, and the ghrelin cells are closed-type cells in frogs (Figure (c)) and turtles (Kaiya et al.,...
Hunger hormone: Ghrelin

Ghrelin cells in rainbow trout were found to be localized as closed-type cells and opened-type cells in the gastric mucosa (Figure (d)). The second area was found in the central nervous system where neuronal cell groups release ghrelin in a synaptic transmission. Since ghrelin was determined to be implicated in the regulation of appetite, it was not surprising to find abundant ghrelin in the arcuate nucleus of the hypothalamus which also is a region rich in GHRH neurons (Kojima et al., 1999). Elsewhere, in the CNS, ghrelin was also present. Immunoreactive neurons were observed in a continuum filling the internuclear space between the paraventricular, arcuate, ventromedial, and dorsomedial hypothalamic nuclei, the perifornical region, and the ependymal layer of the third ventricle. (Cowley et al., 2003) Interestingly, these novel cell groups of ghrelin immunoreactive neurons did not overlap with any of the known cell populations implicated in energy homeostasis, thus suggesting new functions.

Ghrelin has also been identified in the placenta, at an organ that contains all the main regulatory components of the somatotrope axis, i.e., GH, GHRH, SST, IGF-I, and ghrelin. Although, placental expression of ghrelin changes significantly throughout pregnancy, (Gualillo et al., 2001) and is involved in the decidualization of human endometrial stromal cells, the physiological function of this new hormone in the placenta is unknown. The pituitary, heart, kidney, endocrine pancreas, gonads, lungs, and lymphocytes all express ghrelin in low amounts.

DEVELOPMENT OF GHRELIN CELLS IN THE GASTROINTESTINAL TRACT

Ghrelin cells were found to be expressed in the fetal stomach from embryonic day 18 and the number of fetal gastric ghrelin cells increased as the stomach grew, with gastric ghrelin content also increasing with advance of age (Hayashida et al., 2002). Detailed study showed that ghrelin-immunopositive cells appeared in the glandular base of the fundic gland at 1 week of age and they were found in the glandular base and the glandular neck at 3 weeks of age. Then the distribution of ghrelin cells was extended from the glandular base to the glandular neck during the postneonatal developmental period (Sakata et al., 2002). Walia et al., (2009) have also reported that ghrelin-immunoreactive cells were rare at embryonic day 21 and that their number increased progressively until weaning. Gastric ghrelin mRNA levels also increased in an age-dependent manner similar to the number of ghrelin cells (Gualillo et al., 2001, Hayashida et al., 2002). In addition, ghrelin cells in female rats differentiated at an earlier stage of development than that in male rats, and the density of ghrelin cells in female rats was also higher than that in male rats (Sakata et al., 2002). In humans, plasma ghrelin level was also higher in females than in males (Akamizu et al., 2005).

CONTROL OF SECRETION

When sleep is decreased the amount of this hormone is increased. But in the case of this particular hormone, when energy is low, as in the case of reduced sleep, the nervous system is trying to create energy to make up for it. So it assists in creating the hunger hormone to get you to eat more to create more energy. Circulating ghrelin levels depend on acute and chronic changes in energy balance, fasting increasing and feeding decreasing its concentrations. (Hayashida et al., 2001) demonstrated that plasma ghrelin levels in the cow are reduced 1 h after feeding and return to prefeeding levels within 4 h. Also, in rat 48 h starvation resulted in increased plasma ghrelin (Wren et al., 2000). In food-deprived weanling pigs, (Salfen et al., 2003) recently demonstrated a short-lived suppression of plasma ghrelin (at 12 h), followed by an increase at 30–36 h. Other hormones that influence its secretion include estrogen and leptin. Ghrelin is released in a circadian manner prior to the onset of mealtimes. This pattern is illustrated in the graph below.

Blood concentrations of ghrelin are lowest shortly after consumption of a meal, then rise during the fast just prior to the next meal. The figure to the right shows this pattern based on assays of plasma ghrelin in 10 humans during the course of a day.

GHRELIN SECRETION AND ACTION

Ghrelin is secreted during fasting and decreases after feeding. Gastrin and cholecystokinin also enhances ghrelin secretion from stomach, while somatostatin, thyroid, insulin, and GH reduce gastric ghrelin secretion.
Ghrelin promotes secretion of GH by stimulating somatotropes (GH synthesizing cells) in anterior pituitary. Another major action is the regulation of food intake. It increases food intake by increasing appetite through feeding center in hypothalamus. It also stimulates gastric emptying. It also appears to effect the function of the cardiovascular system positively in a variety of ways, such as by increasing cardiac output.

**MECHANISM OF ACTION**

Ghrelin has emerged as the first identified circulating hunger hormone. Ghrelin and synthetic ghrelin mimetics (the growth hormone secretagogues) increase food intake and increase fat mass (Tschoëp et al., 2000, Lall et al., 2001) by an action exerted at the level of the hypothalamus. They activate cells in the arcuate nucleus that include the orexigenic neuropeptide Y (NPY) neurons (Dickson and Luckman, 1997). Ghrelin-responsiveness of these neurons is both leptin- and insulin-sensitive (Hewson et al., 2002). Ghrelin also activates the mesolimbic cholinergic-dopaminergic reward link, a circuit that communicates the hedonic and reinforcing aspects of natural rewards, such as food, as well as of addictive drugs, such as ethanol (Jerlhag, 2007).

Control of energy balance by two types of arcuate nuclei: 1) (POMC) neurons that release alpha melanocyte-stimulating hormone and cocaine & amphetamine-regulated transcript (CART), decreasing food intake & decreasing energy expenditure; 2) neurons that produce agouti-related protein (AGRP) & neuropeptide-Y (NPY), increasing food intake & reducing energy expenditure. alpha-MSH released by pome neurone stimulates melonocortin receptors (MCR-3 & MCR-4) in the paraventricular nuclei (PVN), which then actante neuronal pathways that project nucleus tractus solitarios (NTS) & increase sympathetic activity & energy expenditure. AGRP acts as an antagonist of MCR-4. insulin, leptin & CCK are hormones that inhibit AGRP-NPY neurons & stimulate adjacent POMC – CART neurons, thereby reducing food intake. ghrelin the hormone secreted from the stomach, activates AGRP-NPY neurons & stimulate food intake LePR, leptin receptor; Y1R, neuropeptide receptor.

There is also strong evidence that ghrelin has a peripheral appetite modulatory effect on satiety by affecting the mechanosensitivity of gastric vagal afferents, making them less sensitive to distension resulting in over eating (Page et al., 2007).

**FUNCTION**

**Gastrointestinal tract**

In the gastrointestinal system, ghrelin stimulates emptying of the gastric system. Ghrelin has been proposed as a hormone which promotes intestinal cell proliferation and inhibits its apoptosis during inflammatory states and oxidative stress (Waseem et al., 2008). It also suppresses the pro-inflammatory mechanisms and augments anti-inflammatory mechanisms thus creating a possibility of its therapeutic use in various gastrointestinal inflammatory conditions including colitis, ischemia reperfusion injury and sepsis. In fact, animal models of colitis, ischemia reperfusion and sepsis related gut dysfunction have been shown to be benefited with therapeutic doses of ghrelin (Gonzalez-Rey et al., 2006, Wu et al., 2008). It has also been shown to have regenerative capacity and is beneficial in case of mucosal injury to the stomach (Işeri et al., 2005).
Motilin appears to promote gastrointestinal and pancreatic malignancy (Duxbury et al., 2003, Waseem T, 2009).

In addition, research seems to demonstrate that ghrelin suppresses the utilization of fat in the adipose tissue. In essence, ghrelin appears to be at least partially responsible for letting the body know when it is hungry and for keeping the body informed about the energy balance of the brain and the body.

**Stimulation of growth hormone secretion**

Ghrelin, as the ligand for the growth hormone secretagogue receptor, potently stimulates secretion of growth hormone. The ghrelin signal is integrated with that of growth hormone releasing hormone and somatostatin to control the timing and magnitude of growth hormone secretion.

**Regulation of energy balance**

In both rodents and humans, ghrelin functions to increase hunger through its action on hypothalamic feeding centers. This makes sense relative to increasing plasma ghrelin concentrations observed during fasting. Additionally, humans injected with ghrelin reported sensations of intense hunger. Ghrelin also appears to suppress fat utilization in adipose tissue, which is somewhat paradoxical considering that growth hormone has the opposite effect. Overall, ghrelin seems to be one of several hormonal signals that communicates the state of energy balance in the body to the brain.

Given the effects of ghrelin on energy metabolism and hunger, it is a prominent target for development of anti-obesity treatments. It has been reported that immunization of rats against ghrelin resulted in decreased weight gain and adiposity relative control rats, even though both groups consumed an equivalent amount of food. This intriguing experiment suggests the possibility of a vaccine against obesity.

**Lung development**

In fetuses, it seems that ghrelin is produced early by the lung and promotes growth (Santos et al., 2006).

**Learning and memory**

This hormone also has an effect on brain function. It appears to play a large part in neurotroph, especially as it applies to the hippocampus. Animal model indicates that ghrelin may enter the hippocampus from the bloodstream, altering nerve-cell connections, and so enhancing learning and memory. It is suggested that learning may be best during the day and when the stomach is empty, since ghrelin levels are higher at these times. In addition, ghrelin is important in helping the brain make cognitive adaptations and other changes in response to the environment. Therefore, it is critical to the learning process.

**Stress-induced depression**

The hormone might help defend against symptoms of stress-induced depression and anxiety (Lutter et al., 2008). To test whether ghrelin could regulate depressive symptoms brought on by chronic stress, the researchers subjected mice to daily bouts of social stress, using a standard laboratory technique that induces stress by exposing normal mice to very aggressive “bully” mice. Such animals have been shown to be good models for studying depression in humans. The researchers stressed both wild-type mice and altered mice that were unable to respond to ghrelin. They found that, after experiencing stress, both types of mice had significantly elevated levels of ghrelin that persisted at least four weeks after their last defeat encounter. The altered mice, however, displayed significantly greater social avoidance than their wild-type counterparts, indicating an exacerbation of depression-like symptoms. They also ate less than the wild-type mice.

**Sleep-Duration**

Taheri et al., (2004) suggests that short sleep duration is associated with high levels of ghrelin and obesity; ghrelin appears to be a factor contributing to the short sleep duration and obesity. Scientists have uncovered an inverse relationship between the hours of sleep and blood plasma concentrations of ghrelin; as the hours of sleep increase, ghrelin concentrations were considerably lower, thereby potentially reducing appetite and avoiding potential obesity.

**Cardiovascular system**

It also appears to effect the function of the cardiovascular system positively in a variety of ways, such as by increasing cardiac output. In a totally different perspective, a most promising report is that both ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocyte and endothelial cells (Baldanzi, et al., 2002). These data support the protective actions of ghrelin on the cardiovascular system, and possibly more importantly, that there may be biological actions for the deacylated molecule.

**On other hormonal systems and non endocrine structures**

Ghrelin also may be involved in the neuroendocrine and behavioral response to stress, and in reducing LH secretion (Furuta et al., 2001). Ghrelin and its functional receptor have been shown in testicular tissue to inhibit testosterone secretion, as well as in both the rat and human ovary, suggesting that ghrelin may be responsible in part for the energy homeostasis associated with control of reproduction. (Kishimoto et al., 2003; Gaytan et al., 2003). Ghrelin mRNA and ghrelin receptor mRNAs are expressed in gastric, thyroid, breast and lung neoplasias. This opens potential new routes of treatment.

**Hormone linked to nose’s ability to locate food**

The hormone ghrelin, known to promote hunger and fat storage, has been found to enhance exploratory “sniffing” in both animals and humans.

**CLINICAL SIGNIFICANCE**

Ghrelin levels in the plasma of obese individuals are lower than those in leaner individuals (Cummings et al., 2002) except in the cases of Prader-Willi syndrome-induced obesity and hypothalamic obesity. Those suffering from the eating disorder anorexia nervosa have high plasma levels of ghrelin compared to both the constitutionally thin and normal-weight controls (Germain et al. 2007). These findings suggest that ghrelin is inversely related to calorie intake. Contrary to this, the use of Ghrelin on Anorexia Nervosa patients has been shown to increase food intake by 12-36% over the trial period (Hotta et al., 2009).
Yildiz et al. (2004) found that the level of ghrelin increases during the time of day from midnight to dawn in thinner people, suggesting a flaw in the circadian system of obese individuals. Professor Cappuccio of the University of Warwick has recently discovered that short sleep duration may also lead to obesity, through an increase of appetite via hormonal changes. Lack of sleep produces ghrelin, which stimulates appetite and creates less leptin, which, among its many other effects, suppresses appetite. Ghrelin levels are also high in patients that have cancer-induced cachexia (Garcia et al., 2005), Prader-Willi syndrome is also characterized by high fasting levels of ghrelin; here the ghrelin levels are associated with high food intake (Goldstone et al., 2004).

At least one study found that gastric bypass surgery not only reduces the gut's capacity for food but also dramatically lowers ghrelin levels compared to both lean controls and those that lost weight through dieting alone (Cummings et al., 2002). Ghrelin through its receptor increases the concentration of dopamine in the substantia nigra, a region of the brain where dopamine cell degeneration leads to Parkinson's disease. Hence ghrelin may find application in slowing down the onset of Parkinson’s disease (Andrews et al., 2009).

Also it is linked to reduced fertility, ghrelin decreases the HOXA 10 gene that is involved in developmental programming of the uterus. The HOXA 10 gene determines how the uterus will develop in adulthood. "When you're obese, ghrelin levels are lower, and based on these preliminary findings, they may result in lower fertility," said lead author on the abstract, Hugh S. Taylor, M.D., professor in the Department of Obstetrics, Gynecology & Reproductive Sciences and section chief of Reproductive Endocrinology and Infertility at Yale School of Medicine.

**Anti-Obesity Vaccine**

Given the effects of ghrelin on energy metabolism and hunger, it is a prominent target for development of anti-obesity treatment. Recently, research scientists have developed an anti-obesity vaccine, which is directed against the hormone ghrelin in rodents (Zorilla et al., 2006) and pigs (Vizcarra et al., 2007). The vaccine uses the immune system, specifically antibodies, to bind to selected targets, directing the body's own immune response against them. This prevents ghrelin from reaching the central nervous system, thus producing a desired reduction in weight gain.

**CONCLUSION**

As ghrelin anticipates the initiation of meals and releases GH, one could share the teleological view that ghrelin integrates anabolic changes in the body. In catabolic situations, raised ghrelin levels may induce a combination of enhanced food intake, increased gastric emptying and food assimilation coupled with GH levels which promote a prompt nutrient incorporation into muscles and to fat. These actions of ghrelin are the opposite of leptin which reduces food intake and selectively eliminates fat mass. Thus, both peptides may act as physiological regulators of energy balance. Interestingly, each comes from a peripheral organ (stomach and white adipose tissue respectively). Furthermore, with conceptual incorporation of ghrelin into the group of physiological regulators of GH (i.e., GHRH, somatostatin, IGF-I), we may be on the verge of understanding better aspects of the regulation of secretion of GH that previously were not understood. In addition, characteristics of ghrelin cells in the stomach and other parts of the gastrointestinal tract are different; closed-type ghrelin cells are localized in the stomach and many opened-type ghrelin cells are localized throughout the small and large intestines. Since the length of the gastrointestinal tract is long, considerable amounts of plasma ghrelin can be assumed to be derived from ghrelin cells in small and large intestines. Further studies are needed to understand the physiological and pathological roles of ghrelin cells in both small and large intestines. Moreover, posttranscriptional modifications are very important for physiological active ghrelin, necessitating the need to understand how GOAT is involved in the regulation of ghrelin biosynthesis and consequently may be important for controlling ghrelin cells in some physiological states.

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