Ghrelin

Ghrelin is a hormone produced mainly by P/D1 cells lining the fundus of the human stomach and epsilon cells of the pancreas that stimulates appetite. 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. Ghrelin is also produced in the hypothalamic arcuate nucleus where it stimulates the secretion of growth hormone from the anterior pituitary gland. In some bariatric procedures, the level of ghrelin is reduced in patients, thus causing satiation before it would normally occur.

Structure of Ghrelin and Its Receptor

Ghrelin exists in an endocrinological inactive (pure peptide) and an active (octanoylated) form (see Hexatropin). Other side chains than octanoyl were also observed.

Ghrelin is synthesized as a preprohormone, then proteolytically processed to yield a 28-amino acid peptide. An interesting and unique modification is imposed on the hormone during synthesis in the form of an n-octanoic acid bound to one of its amino acids; this modification is necessary for biologic activity.

Synthesis of ghrelin occurs predominantly in epithelial cells lining the fundus of the stomach, with smaller amounts produced in the placenta, kidney, pituitary and hypothalamus.

The ghrelin receptor was known well before ghrelin was discovered. Cells within the anterior pituitary bear a receptor that, when activated, potently stimulates secretion of growth hormone - that receptor was named the growth hormone secretagoue receptor (GHS-R). The natural ligand for the GHS-R was announced in 1999 as ghrelin, and ghrelin was named for its ability to provoke growth hormone secretion (the suffix ghre means "grow").

Ghrelin receptors are present on the cells in the pituitary that secrete growth hormone, and also have been identified in the hypothalamus, heart and adipose tissue. Receptors for ghrelin are expressed by neurons in the arcuate nucleus and the ventromedial hypothalamus. The ghrelin receptor is a G protein-coupled receptor, formerly known as the GHS receptor (growth hormone secretagogue receptor). Ghrelin is also made by a small population of neurons in the arcuate nucleus. Ghrelin plays a significant role in neurotrophy, particularly in the hippocampus, and is essential for cognitive adaptation to changing environments and the process of learning.[3] Recently, ghrelin has been shown to activate the endothelial isoform of nitric oxide synthase in a pathway that depends on various kinases including Akt.

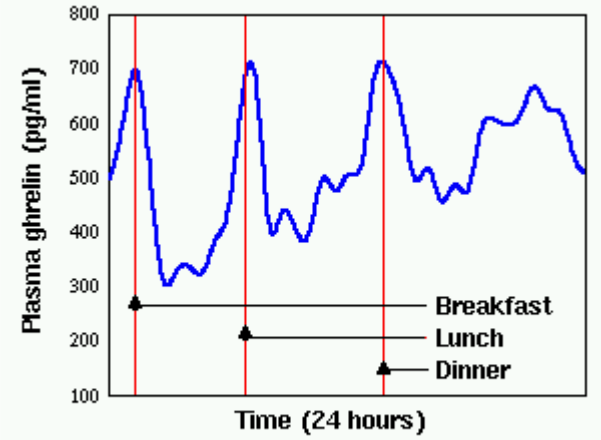
Control and Physiologic Effects of Ghrelin

At least two major biologic activities have been ascribed to ghrelin:

- 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 though its action on hypothalamic feeding centers. This makes sense relative to increasing plasma ghrelin concentrations observed during fasting (see below). 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 communicate the state of energy balance in the body to the brain.

Other effects of ghrelin include stimulating gastric emptying and having a variety of positive effects on cardiovascular function (e.g. increased cardiac output). It is not totally clear whether the cardiovascular effects are a direct effect of ghrelin or represent an indirect effect of ghrelin's ability to stimulate growth hormone secretion.

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.



Adapted from Cummings et al. Diabetes 50:1714, 2001.

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.

Mechanism of action

Ghrelin has emerged as the first circulating hunger hormone. Ghrelin and synthetic ghrelin mimetics (the growth hormone secretagogues) increase food intake and increase fat mass by an action exerted at the level of the hypothalamus. They activate cells in the arcuate nucleus that include the orexigenic neuropeptide Y (NPY) neurones. Ghrelin-responsiveness of these neurones is both leptin and insulin sensitive. 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.

Disease States

Ghrelin levels in the plasma of obese individuals are lower than those in leaner individuals. Those suffering from the eating disorder anorexia nervosa appear to have high plasma levels of ghrelin. These findings suggest that ghrelin does not cause anorexia or obesity, rather, ghrelin attempts to correct these disorders. Yildiz and colleagues 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, amongst its many other effects, suppresses appetite. However, this study does not explain the low levels of Ghrelin found in the obese population. In the fetuses, it seems that ghrelin is produced early by the lung and promotes its growth. Ghrelin levels are also high in patients who have cancer-induced cachexia (general physical wasting and malnutrition).

Ghrelin concentrations in blood are reduced in obese humans compared to lean control subjects, but whether this is cause or effect is not defined. Patients with anorexia nervosa have higher than normal plasma ghrelin levels, which decrease if weight gain occurs.

Prader-Willi syndrome is another disorder relevant to ghrelin science. Affected patients develop extreme obesity associated with uncontrollable and voracious appetite. The plasma ghrelin levels are exceptionally high in comparison to patients similarly obese due to other causes. Prader-Willi syndrome is clearly a complex disease with many defects; it may be that excessive ghrelin production contributes to the appetite and obesity components. Prader-Willi syndrome is

also characterized by high fasting levels of ghrelin; here the ghrelin levels are associated with high food intake.

Animal models indicate that ghrelin may enter the hippocampus from the bloodstream, 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 rodents, X/A-like cells produce ghrelin.

Relation to obestatin

Obestatin is a hormone that was found, in late 2005, to *decrease* appetite. Both obestatin and ghrelin are encoded by the same gene; the gene's product breaks apart to yield the two peptide hormones. The purpose of this mechanism is unknown.

Anti-obesity vaccine

Recently Scripps research scientists have developed an anti-obesity vaccine, which is directed against the hormone ghrelin. 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.

Plasma Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass Surgery

At least one study found that gastric bypass surgery not only reduces the gut's capacity for food, but also dramatically lowers ghrelin levels. Weight loss causes changes in appetite and energy expenditure that promote weight regain. Ghrelin is a hormone that increases food intake in rodents and humans. If circulating ghrelin participates in the adaptive response to weight loss, its levels should rise with dieting. Because ghrelin is produced primarily by the stomach, weight loss after gastric bypass surgery may be accompanied by impaired ghrelin secretion.

Methods We determined the 24-hour plasma ghrelin profiles, body composition, insulin levels, leptin levels, and insulin sensitivity in 13 obese subjects before and after a six-month dietary program for weight loss. The 24-hour ghrelin profiles were also determined in 5 subjects who had lost weight after gastric bypass and 10 normal-weight controls; 5 of the 13 obese subjects who participated in the dietary program were matched to the subjects in the gastric-bypass group and served as obese controls.

Results Plasma ghrelin levels rose sharply shortly before and fell shortly after every meal. A diet-induced weight loss of 17 percent of initial body weight was associated with a 24 percent increase in the area under the curve for the 24-hour ghrelin profile ($P=0.006$). In contrast, despite a 36 percent weight loss after gastric bypass, the area under the curve for the ghrelin profile in the gastric-bypass group was 77 percent lower than in normal-weight controls ($P<0.001$) and 72 percent lower than in matched obese controls ($P=0.01$). The normal, meal-related fluctuations and diurnal rhythm of the ghrelin level were absent after gastric bypass.

Conclusions The increase in the plasma ghrelin level with diet-induced weight loss is consistent with the hypothesis that ghrelin has a role in the long-term regulation of body weight. Gastric bypass is associated with markedly suppressed ghrelin levels, possibly contributing to the weight-reducing effect of the procedure.

Science Daily (May 10, 2006) — Ghrelin, a hormone long considered a key player in obesity, may instead take a major role in maintaining the balance between insulin and glucose and the development of diabetes, said Baylor College of Medicine researchers in a report in the current issue of the journal Cell Metabolism.

"Everybody has been pushing the connection between obesity and ghrelin," said Dr. Roy G. Smith, director of the BCM Huffington Center on Aging, "Companies have been developing ghrelin

antagonists as anti-obesity drugs. Now these drugs may have a value in treating diabetes."

The downside is that the drugs may not forestall obesity.
In studies in his laboratory, mice bred to be deficient in both ghrelin (which stimulates appetite) and leptin (associated with controlling obesity) could be expected to be thin or of normal body weight, said Smith, also a professor of Molecular and Cellular Biology at BCM. That was a surprise, said the paper's first author, Dr. Yuxiang Sun, a BCM instructor in the center. "They were just as fat as the mice bred to lack only leptin," said Smith. However, their glucose levels were lower than in leptin-deficient mice. When Sun did a glucose tolerance test on the mice, she found much lower levels in the animals that did not produce either ghrelin or leptin.

"They were more resistant to glucose because they secreted more insulin in response to the glucose challenge," said Smith.
When Sun and Smith investigated further, they found lower levels of uncoupling protein-2 (Ucp2) in cells called pancreatic islets (where insulin is made). Reducing Ucp2 improves the cell's ability to make ATP, the cell's energy molecule, thereby increasing the sensitivity of the pancreatic beta cell (the cell in the pancreas which produces insulin) to glucose-induced insulin release. Further tests in animals lacking ghrelin, showed that besides increased insulin secretion, their sensitivity to insulin was increased, said Sun. "That means glucose was cleared more efficiently."

While Smith sees a role for drugs that block ghrelin in treatment of type 2 diabetes (which usually occurs in adulthood and is often associated with obesity), he sounds a cautionary note.
"If through this process, you increase ATP production by the beta cell, you may in the long-term get oxidative stress which could eventually destroy the beta cell," he said. He said he does not yet have data to determine whether that is true or not.

In an accompanying analysis, Dr. Rexford S. Ahima of the University of Pennsylvania School of Medicine, wrote, "Overall, the studies provide compelling evidence that ghrelin has unique dual effects on glucose homeostasis (the balance between glucose and insulin), at least in a genetic model. Ghrelin antagonism (or blocking) may be a new approach for treating type 2 diabetes by improving insulin secretion in response to glucose and enhancing peripheral insulin action. The challenge is to ascertain if these results in rodents can be translated to patients."

Eating and sleeping—their relationship to ghrelin and leptin.

EATING AND SLEEPING are two kinds of behavior that are essential for the survival of humans and higher animals. Whereas it is obviously excluded that they occur exactly at the same time, there appear to be common regulators of both phenomena. With the identification of ghrelin as the endogenous ligand of the growth hormone (GH)-secretagogue (GHS) receptor by Kojima et al. a new endogenous regulator of food intake and possibly also of sleep was found. In this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, Bodosi et al. report a sophisticated study on the relationship between sleep, feeding, ghrelin, and its antagonist in the energy balance, leptin.

The detection of ghrelin was preceded in the 1970s by the synthesis of GHSs and by the cloning of the GHS receptor. Although they act on a different receptor, the GHSs and ghrelin share the capacity of GH-releasing hormone (GHRH) to stimulate GH. In addition to this endocrine effect, GHRH stimulates non-rapid eye movement (REM) sleep in various species including humans. Similarly sleep-promoting effects of synthetic GHS were found in humans. Furthermore, some hints exist for a stimulating influence of GHS on food intake and body weight.

Soon after the identification of ghrelin, which is displayed mainly in the stomach and also in other tissues including the hypothalamus, it became clear that it is the most powerful endogenous orexigenic

factor known so far. Ghrelin stimulates food intake and conserves fat, resulting in increasing body weight in rodents. Similarly, appetite and calorie intake increased after ghrelin administration in humans. Ghrelin levels were found to be changed in eating disorders, with high concentrations in anorexia and Prader-Willi Syndrome and blunting in obesity. In contrast to ghrelin, leptin is an anorexigenic factor and it is thought that ghrelin and leptin regulate the energy balance in a reciprocal fashion.

Similarly to GHRH, non-REM sleep was enhanced after ghrelin in mice and humans. Intact GHRH receptors were shown to be the prerequisite for this effect in mice. Also, an effect of leptin on sleep was reported. Bodosi et al. compared plasma ghrelin and leptin levels and hypothalamic ghrelin contents, sleep, brain temperature, and feeding throughout the dark-light cycle in rats in three experimental conditions: free-feeding animals with normal diurnal rhythms, restricted feeding, and sleep deprivation. From their findings they conclude that intimate relations between feeding and plasma ghrelin and leptin are corroborated, whereas there are no strong links between sleep and these hormones in the rat. These study results are a challenge to search for the answers to new questions.

To what extent is ghrelin secretion under circadian regulation? In humans there exist controversial data whether ghrelin levels show major fluctuations throughout the day.

Whereas the fluctuations of hypothalamic ghrelin were not significantly under baseline conditions, according to the localization of ghrelin-containing neurons in the brain, Cowley et al. suggested a role of ghrelin in the regulation of rhythms, particularly in the timing of meals. Does ghrelin also play a role in the timing of sleep? This is not supported convincingly by the findings in the rat.

Sleep deprivation in the rat is accompanied by increases in ghrelin levels. In contrast, in humans a nocturnal ghrelin peak was found to be blunted during sleep deprivation. Findings in humans suggest

dose-dependent differences in the behavioral effects of ghrelin. At night, a higher dose of ghrelin significantly induced hunger, whereas the lower dose promoted sleep. Interestingly, leptin peaks in humans and in rats during the night, whereas they have opposite sleep-wake patterns. Are there differences in the action of ghrelin and leptin between rats and humans?

So far little is known about gender differences in the effects of ghrelin. Given the fact that GHRH exerted sexually dimorphic effects on sleep-endocrine activity in humans similar studies appear to be necessary with ghrelin.

The GHS receptor appears to be an interesting target for pharmacological regulation of food intake, particularly for the treatment of obesity. During the development of such therapies side effects on sleep must be kept in mind.