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# Ghrelin: Update 2003

*Ghrelin is a recently described peptide hormone that is secreted by endocrine cells in the gastrointestinal tract. Although its initial discovery was as a novel growth hormone secretagogue, it has been found to regulate feeding behavior by modulating expression levels of orexigenic peptides in the hypothalamus. Ghrelin has been implicated in the coordination of energy balance and weight regulation, and its dysregulation may be important in obesity. Ghrelin also has several other physiologic actions besides potential regulation of food intake that are described in this brief review.*

Key Words: ghrelin, peptide, hormone, energy regulation, obesity



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The prevalence of obesity (defined as body mass index [BMI, kg/m$^2$] $\geq$30) in U.S. adults has almost doubled in the last 20 years.[1] Approximately 25% of the U.S. population is therefore considered obese, whereas more than 60% is overweight (including those who are obese), which is defined as a BMI $\geq$25.[2] Obesity is associated with adverse health effects including increased total mortality,[3] and it is an independent risk factor for diabetes and cardiovascular disease, among other comorbidities. Although the pathogenesis of obesity is clearly multifactorial, recent research has revealed a number of potentially important candidates. Ghrelin is one of several peptide hormones secreted by the gastrointestinal tract that is implicated in the coordination of eating behavior and weight regulation. Initially, ghrelin was discovered as the endogenous ligand to the hypothalamic growth hormone (GH) secretagogue receptor,[4] although it was soon established that ghrelin has a role in weight regulation because its administration increases food intake and causes fat and weight gain in rodents.[5] Interest in this hormone has intensified with the publication of a recent paper[6] suggesting that ghrelin suppression could ameliorate the success of gastric bypass, a surgical method to reduce obesity.

This review was prepared by Julie Eisenstein, M.D., and Andrew Greenberg, M.D., Energy Metabolism Lab, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA.

Ghrelin is a post-translationally modified (octanoylated), 28–amino acid peptide[4] that is secreted by a number of endocrine cells in the body, primarily the X/A oxyntic cells in the stomach.[7] The *n*-octanoyl group on the serine 3 residue is essential for its activity. Ghrelin acts to regulate feeding, a role that is independent of its GH stimulation. There is evidence that ghrelin's orexigenic effects are mediated by the hypothalamic hormones neuropeptide Y (NPY) and agouti growth–related peptide (AGRP).[8] Specifically, animal studies have demonstrated that hypothalamic NPY[9] and AGRP[10] mRNA levels increase after ghrelin administration and that the orexigenic effect is maintained even in mice that lack NPY.[11]

Chronic exogenous administration of ghrelin in rodents leads to an increase in body weight. In humans, long-term outcomes are not available, but cross-sectional data demonstrate that higher plasma ghrelin levels are associated with lower body weight;[12] this suggests that ghrelin is up-regulated by weight loss and therefore acts to maintain body weight in a steady state. People with anorexia nervosa have an inappropriately high plasma ghrelin given their dietary restraint; Otto et al. suggested the possibility of ghrelin resistance in this population.[13]

Short-term studies further highlight ghrelin's role in energy balance. In rodents, exogenous ghrelin has been shown to signal meal initiation. In one study,[9] ghrelin caused a significant and dose-related increase in cumulative food intake in rats when administered intracerebroventricularly, even in those rats who were GH deficient, suggesting that the feeding behavior function of ghrelin is independent of its GH-stimulating function. In humans, ghrelin is up-regulated with short-term fasting,[14] and in single-meal studies, an increase in plasma ghrelin coincides with the initiation of food intake (ghrelin levels fall postprandially).[15] Over the course of the day, plasma ghrelin is up- and down-regulated in the setting of decreased and increased food intake, respectively;[14] again, this is consistent with a possible role for ghrelin in long-term energy balance and weight regulation. Evidence exists, however, that obese subjects do not exhibit the decline in plasma ghrelin that is seen after a meal in the lean.[16] This dysregulation of ghrelin production may, in part, contribute to weight gain in this population. Some of the metabolic effects of exogenous ghrelin administration in animals and humans are outlined in Table 1.

**Table 1.** Metabolic Effects of Ghrelin Administration

| Effect | Animal Studies | Human Studies |
|---|---|---|
| Hormones | | |
| GH | Increases[4,7,17] | Increases[18–20] |
| ACTH | Increases[17] | Increases[18] |
| TSH | Decreases[17] | No change[18] |
| NPY | Increases[8–10,21,22] | |
| AGRP | Increases[8,10] | |
| Insulin | Increases[23] | Decreases[24] |
| Energy Measures | | |
| Food intake | Increases[9,17,21,25,26] | Increases[28] |
| Weight | Increases[5,8,25,27] | |
| Adiposity | Increases[5,25] | |
| Body temperature | Decreases[4] | |

GH = growth hormone, ACTH = adrenocorticotrophic hormone, TSH = thyroid-stimulating hormone, NPY = neuropeptide Y, AGRP = agouti growth-related peptide.

Ghrelin also appears to be regulated by dietary composition. In animals, one group[23] found that ghrelin decreased with ingestion of a high-fat diet and increased with intake of a low-protein diet over a 30-day period. Similarly, another group[29] found that the 14-day consumption of a high-fat diet was associated with decreased ghrelin levels in comparison with that of a control diet, prompting these investigators to postulate that fat ingestion might serve as a counterregulatory mechanism to limit the development of diet-induced adiposity. It appears that the intake of macronutrients that promote weight gain might decrease ghrelin, and intake that promotes poor growth (e.g., a low-protein diet) may up-regulate ghrelin.

Recently, Cummings et al.[6] studied 24-hour plasma ghrelin profiles in obese subjects undergoing diet-induced weight loss, in patients undergoing gastric bypass surgery, and in normal-weight controls. Gastric bypass surgery is a procedure gaining popularity for the treatment of morbid obesity, primarily because of its success in maintaining weight loss.[30] Although serum glucose levels appear to regulate ghrelin,[31] nutrient contact with the stomach cells, rather than cellular nutrient utilization, may be more important in inhibiting ghrelin release because the administration of intravenous insulin does not suppress ghrelin.[32] Gastric distention does not seem to be a primary mediator in ghrelin release; one study[5] demonstrated that oral gavage with water elicited no change in ghrelin levels in rodents. Because ghrelin is a stomach hormone whose secretion may be disrupted during procedures such as the proximal Roux-en-Y gastric bypass, Cummings et al. hypothesized that the effect may contribute to the prolonged weight loss and maintenance seen in patients that have undergone this procedure. As predicted, the area under the curve for plasma ghrelin was 77% lower in those who had undergone gastric bypass surgery than in normal-weight controls, and 72% lower than in the matched obese controls over 24 hours. Additionally, the subjects in the gastric bypass group lost the fluctuations of plasma ghrelin that typically precede and follow meals. By contrast, obese subjects who had undergone diet-induced weight loss retained similar patterns of 24-hour ghrelin curves, although they had significantly higher plasma ghrelin levels at all time points measured and, therefore, a greater plasma ghrelin area under the curve. The benefits of lower plasma ghrelin seen in the surgically treated subjects can be inferred by other human studies demonstrating that exogenously administered ghrelin causes increased hunger and energy intake.[28] However, it is unclear from Cummings et al. whether the ghrelin suppression seen in the subjects who underwent gastric bypass surgery correlates with decreased hunger or improved long-term weight loss outcomes. In addition, in under- and overfeeding conditions the concentration of baseline plasma ghrelin seems to exhibit no relationship with the magnitude of body weight change.[33] Further studies are needed to determine whether ghrelin profiles can predict who will have successful gastric bypass surgery.

Although ghrelin may be a future pharmacologic target in the treatment of obesity, the multiple metabolic effects of ghrelin beyond its role as an orexigenic agent may limit the use of an antagonist. In particular, because ghrelin is a potent GH secretagogue, interrupting release of GH via ghrelin antagonism may be detrimental to cell growth and metabolism. It also appears that ghrelin has several beneficial effects on the cardiovascular system (Table 2). Given the current interest in caloric restriction and longevity, the possibility that some of the

**Table 2.** How Does Ghrelin Administration Favorably Affect Cardiovascular Function?

| Effect | Reference |
|---|---|
| Animals | |
| Exogenous administration improves LV function and remodeling (rats with heart failure) | 34 |
| Exogenous administration decreases cardiac cachexia (rats with heart failure) | 34 |
| Humans | |
| Exogenous administration improves forearm blood flow (healthy people) | 35 |
| Exogenous administration decreases mean arterial pressure (healthy men) | 36 |
| Exogenous administration increases cardiac index and stroke volume (healthy men) | 36 |

LV = left ventricle.

benefits of caloric restriction beyond that of weight loss may be mediated by increased ghrelin levels, or that decreased ghrelin in obesity may contribute to the risk for hypertension or congestive heart failure, is intriguing. In the future, exogenous ghrelin may be used in the treatment of people with cardiac cachexia.

Further complicating the therapeutic considerations of ghrelin and weight control is the observation of population differences in the relationship between ghrelin levels and body weight. Ghrelin genotype frequencies seem to be similar in extremely obese children and adolescents, underweight students, and normal-weight adults, and none of the gene variants seem to be related to altered weight regulation.[36] Additionally, although plasma ghrelin is lower in obese Caucasians than in lean Caucasians, fasting plasma ghrelin is lower in Pima Indians (a population highly susceptibility to obesity) than in Caucasians, even after adjusting for fasting plasma insulin concentration.[12]

Therefore, further work in this area should better clarify: (a) appropriate populations to target ghrelin manipulation; (b) long-term effects of ghrelin or its antagonists in humans; (c) its potential interference with other hormonal systems; and (d) optimal, or even practical means to manipulate endogenous (or administer exogenous) ghrelin for physiologic benefit. Ultimately, further studies that use pharmacologic ghrelin or its antagonist will determine its role in energy balance and other metabolic sequelae. The elucidation of the role of ghrelin and the myriad other emerging hormones with well-described or postulated effects on hunger, food intake, and weight control is still very much in its infancy. Future research in this area promises to yield exciting discoveries in the field of energy regulation.


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# Body Mass Index and Mortality in Asian Populations: Implications for Obesity Cut-points

*Investigators have questioned whether body mass index (BMI, kg/m$^2$) cut-points for obesity used in the United States and Europe are appropriate for Asian countries. A recent study examined the association between BMI and mortality in a population-based cohort of Japanese men and women. These and other results did not indicate a need for lower cut-points in Asians.*

Key Words: obesity, body mass index, Asians, mortality, reference standards



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Since the publication of the Metropolitan Life Insurance Tables,[1] standards for body weight have been defined by the association between mortality and weight relative to height. In 1998, cut-points for body mass index (BMI, kg/m$^2$) were created by the International Obesity Task Force for the World Health Organization (WHO) to classify weight status and define obesity in adult populations.[2] Increases in mortality associated with a BMI ≥25.0 in Caucasians were the primary rationale behind the WHO cut-points for overweight (≥25.0) and obesity (≥30.0).

Within the past few years, several investigators[3–6] and policy-making organizations[7] have questioned whether the cut-points for obesity currently used in the United States and in most European countries are appropriate for use in Asian countries. Studies examining the association between BMI and mortality in an Asian population are therefore of great interest. One such study was recently published by Tsugane et al.[8] in a population-based cohort of Japanese men and women.

This Japanese cohort was established in 1990 and was composed of 54,498 men and women, who resided in 14 administrative districts, and were 40 to 59 years of age at baseline. Data on height, weight, and several covariates were collected by questionnaire. Validity of

This review was prepared by June Stevens, Ph.D., Departments of Nutrition and Epidemiology, CB 7461, and Eric M. Nowicki, M.P.H., R.D., Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.